

Imaging and Treatment of Acute Ischaemic Stroke -

The Application and Verification of Non-invasive
Imaging Techniques in the Investigation and Treatment
of Acute Ischaemic Stroke

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**"It is incident, I am afraid, in Physicians
above all men, to mistake subsequences for
consequences."**

Samuel Johnson.

Preface

I had little interest in stroke until I chanced upon a letter in the Lancet in 1988 by Henze et al¹ reporting a patient with vertebrobasilar artery thrombosis, who was treated with tissue Plasminogen Activator, with excellent results. To my knowledge, acute ischaemic stroke was one of the main contraindications to the use of thrombolytic therapy for acute myocardial infarction because of the risk of cerebral haemorrhage, so Henze's case report seemed very controversial. Controversy is fascinating, particularly in medical practice. The history of medicine is littered with fundamental dogmas which restricted therapy until systematically examined and thrown out by evidence from good scientific research. The teaching of medicine, which should encourage young enquiring minds, often in my experience produces doctors who are only too happy to follow the teaching of their forebears without question.

So, thrombolysis for acute ischaemic stroke? Why not? As a house officer in 1982, I witnessed the beginning of the modern use of thrombolysis for acute myocardial infarction, and all the controversy that that produced. And yet today, a mere decade later, not only is it established therapy, but there is good information on adverse effects and which drug is best. The mechanism of acute ischaemic stroke (acute arterial occlusion) is the same as the mechanism of acute myocardial infarction. So I began to search the literature

for other reports on thrombolysis in stroke.

At that time (1988/89) there was a very limited amount of information, but in the following year, several moderate sized "open" trials were published. Even with my limited knowledge of statistics and of the natural history of cerebrovascular disease, it seemed to me that the methodology of these "trials" was questionable, and that there were many unknown factors about the natural history of acute ischaemic stroke, such as the relationship between reperfusion and oedema formation.

So I applied for a grant, with a huge amount of assistance from Professor Warlow, to obtain funding to enable me to work full time on acute stroke imaging and thrombolytic treatment for two years. This thesis is the result of that effort. I hope that the results of this project go some way towards solving some of the controversies, and that research on thrombolysis in acute ischaemic stroke is now on a more methodologically sound footing.

I suppose that the acid test of any treatment must be "would the proponents of it take it themselves?". For me, if I had an acute ischaemic stroke, the answer is unequivocally "yes". If it was my mother having the stroke, I'm not so sure(!), and I await with great interest the results of larger multicentre randomised controlled trials of thrombolysis in acute ischaemic stroke now underway.



The non-invasive cerebrovascular imaging equipment used in the studies described in this thesis. On the right is the computer for the gamma camera, and sitting on top of it, the micro computer used to acquire the Mean Cerebral Transit Time studies. At the centre back is the gamma camera used for the Mean Cerebral Transit Time studies. On the left is the EME TC 64B transcranial Doppler ultrasound equipment, for measuring the basal intracranial artery blood velocities, mounted on a standard NHS tea trolley. Also on the same trolley are a Sony video printer for hard copies, a tape recorder for recording long sequences of Doppler signal, ultrasound gel, and (not well seen) a Datex "Normocap" end tidal CO₂ analyser. The trolley was easily transportable to the patient's bedside.

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ABSTRACT OF THESIS (Regulation 3.5.10)

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Title of Thesis THE APPLICATION AND VERIFICATION OF NON-INVASIVE IMAGING TECHNIQUES IN THE INVESTIGATION AND TREATMENT OF ACUTE STROKE

No. of words in the main text of Thesis 85000 words

Abstract of Thesis : The purpose of the project which lead to the writing of this thesis was to:

- 1) Establish the accuracy, limitations and practicality of a simple isotope test, the Mean Cerebral Transit Time (MCTT), developed in the Western General Hospital, Edinburgh, and its ability to diagnose the pattern of cerebral arterial occlusion in acute ischaemic stroke;
- 2) Study the effect of early reperfusion of the cerebral infarct on swelling of the infarct in the acute stage, and clinical outcome in patients with symptoms of extensive acute cerebral ischaemia;
- 3) Perform an overview analysis of thrombolytic therapy for acute ischaemic stroke;
- 4) Set up a pilot randomised controlled trial of intra-arterial thrombolysis in acute ischaemic stroke.

The Thesis is divided into four parts. Part One describes: a) the background to current understanding of the aetiology and pathogenesis secondary treatment of, and possible primary treatments for acute ischaemic stroke; b) the anatomy and physiology of the cerebral circulation; c) imaging methods for investigating the cerebral circulation and brain parenchyma - angiography, ultrasound (TCD), radioisotope methods (particularly the MCTT), SPECT, PET, CT and MRI - and the contribution each has made to improved understanding of stroke pathophysiology.

Part Two describes a study in 120 acute stroke patients (mostly ischaemic) to assess the accuracy of: 1) the Oxfordshire Community Stroke Project Classification (OCSP) of acute stroke; 2) a simple method of classifying cerebral infarcts on CT brain scans; and 3) the MCTT in diagnosing the likely site of cerebral arterial occlusion compared with transcranial Doppler ultrasound. The OCSP clinical classification was very accurate in predicting the site of infarction on the CT brain scan. The CT infarct classification had excellent interobserver agreement for site/extent, swelling, and haemorrhagic transformation of the infarct. The MCTT was as accurate as TCD at diagnosing the likely site of cerebral arterial occlusion. The MCTT was a surprisingly robust and simple diagnostic test.

Part Three is the relationship between reperfusion of the infarct shown by TCD, the amount of swelling in the infarct in the acute stage shown by CT brain scan, and clinical outcome. Clinical outcome at three months was better, and infarct swelling in the acute stage less in 47 patients with symptoms of a large cerebral infarct, with TCD evidence of reperfusion of the infarct in the first few days after the stroke, than in those with no TCD evidence of reperfusion.

Part Four contains a review of all publications on thrombolysis in stroke patients and overview analysis of the randomised controlled trials suggesting that thrombolysis may be beneficial in acute ischaemic stroke. The pilot study of intra-arterial thrombolysis in patients with extensive acute ischaemic stroke is described, with detailed discussion of each patient randomised.

Publications arising from the work in the Thesis so far are included.

The Aims of this Thesis.

The purpose of the project which lead to the writing of this thesis was to:

- 1) Verify the accuracy and establish the limitations and practicality of the isotope mean cerebral transit time technique (MCTT) for diagnosing the pattern of cerebral arterial occlusion in acute ischaemic stroke,
- 2) Devise an imaging strategy for rapid diagnosis of the site and extent of cerebral arterial insufficiency in patients presenting with an acute stroke,
- 3) Clarify the relationship between reperfusion of the cerebral infarct, swelling of the infarct in the acute stage, and clinical outcome in patients with symptoms of extensive acute cerebral ischaemia,
- 4) Discuss the potential of thrombolytic therapy to treat acute ischaemic stroke based on a critical review of the literature on its use to date in stroke patients and the success of thrombolysis in treating vascular disease elsewhere in the body, particularly myocardial infarction,
- 5) Describe the setting up of a small randomised controlled trial of intraarterial thrombolysis in acute ischaemic stroke, and the result of the first year of the trial.

My contribution to this work

I suggested to my colleagues that thrombolysis was worth testing in acute ischaemic stroke in a randomised controlled trial. I was fortunate to be in Edinburgh where Professor Warlow and colleagues have a considerable interest and expertise in stroke.

I obtained ethical permission for the thrombolysis trial and for the imaging studies.

I applied for a grant, with considerable assistance from Professor Warlow to obtain funding to pay my salary and a small amount of extra money to help fund the study.

I performed the transcranial Doppler ultrasound, isotope Mean Cerebral Transit Time and duplex carotid ultrasound studies, and supervised the CT brain scans on the stroke patients. I performed most of the angiograms on the patients randomised in the thrombolysis trial.

I organised the intraarterial thrombolysis trial with a great deal of help from the Neurologists and General Physicians in the Western General Hospital, and the Chief Pharmacist Margaret Braithwaite.

I reviewed the literature on thrombolysis in acute ischaemic stroke, wrote to principal investigators of trials, obtained translations of foreign language papers, and analysed all the available published data on thrombolysis in acute ischaemic stroke using the overview technique.

I analysed the results of the imaging studies, including the setting up of databases, and statistical analysis using computer programs (with advice from Dr J Slattery, statistician).

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advice about the manuscript. Finally, I would like to thank my husband Mark and son Maxwell for their constant support.

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Part One

Chapter One

The History of Stroke : The evolution of the fundamental concepts which underly current understanding of the pathophysiology and epidemiology of stroke.

1.1.1 General introduction

1.1.2 From the Greek Period to 1900

1.1.3 1900 to the 1950s

1.1.4 Modern epidemiological studies

1.1.5 The role of carotid atheroma as a cause of stroke

1.1.6 Cardioembolic stroke

1.1.7 Current understanding of the sequence of events in the
ischaemic brain following cerebral arterial occlusion

1.1.8 Prevention of, and therapeutic options for, acute
ischaemic stroke

Summary of Chapter

1.1.1 General Introduction.

There are disadvantages to studying diseases affecting the brain which in part account for the lag in development of treatments for brain diseases behind those affecting more accessible organs in the body. The brain cannot easily be palpated, or transilluminated, or auscultated, or percussed in any useful way as can hearts, chests and kidneys. Unfortunately the clinical manifestations of brain dysfunction, for example hemiparesis, do not allow one to distinguish between permanently damaged brain and "malfunctioning but viable" brain, until either the malfunctioning brain has recovered or the permanently damaged brain has not.

A further obstacle which has until recently delayed the understanding of brain diseases, is that patients do not always die immediately from the effects of their acute neurological illness. They may succumb weeks later from a secondary illness such as bronchopneumonia, allowing the neurological lesion time to evolve through its natural history, presenting the pathologist with information coloured by time since the event. Add to this the inherent complexity of the brain and the result is a sophisticated puzzle and an enormous challenge - firstly to find out what causes the disease and secondly how to treat it.

With these thoughts in mind, it should be no surprise that so far no effective treatment for acute ischaemic stroke has been found. And yet it is increasingly important

to do so. Stroke is the third commonest cause of death in the Western World and leaves many survivors dependant on others for help in activities of daily living.² There have been major advances in the last 20 years in prevention of ischaemic stroke, for example aspirin³ and carotid endarterectomy⁴ in patients with transient ischaemic attacks (TIAs). But there is still nothing that can be offered to a patient in the acute phase of an ischaemic stroke which will definitely reduce death and disability.

In the last fifty years, understanding of the pathophysiology of acute ischaemic stroke has advanced partly due to the development of less invasive neuro-investigative techniques such as CT scanning. This has made possible study of the brain soon after the acute event with minimal disturbance to the patient. This, coupled with experimental work in animals, means that the mechanisms of brain damage are sufficiently well understood to have prompted trials of many drugs (old and new) in acute ischaemic stroke in the last ten years. Some of these are particularly promising and hopefully it will not be long before we can offer proven treatments to patients who have sustained an acute ischaemic stroke.

Fundamental facts established over thousands of years underly modern understanding of stroke pathophysiology. Recent epidemiological studies have improved knowledge of risk factors for and causes of different types of stroke,

and the magnitude of the problem for health services. Most of the contribution from imaging techniques has come in the twentieth century; current management of stroke patients is dependant on imaging, and future treatment certainly will be. Before discussing neuroimaging methods in detail, the background to present ideas on stroke aetiology, pathogenesis, and epidemiology will be outlined.

1.1.2 From the Greek Period to the 1900s : A brief summary of the early history of clinical aspects and pathophysiology of stroke.

The term "stroke" implies a sudden event with devastating effect outside the control of the individual - as in "struck down by the hand of God". Stroke is not just a disease of modern times. Hippocrates in circa 400 BC recognised that "persons are most subject to apoplexy between the ages of 40 and 60" and "unaccustomed attacks of numbness and anaesthesia are signs of impending apoplexy".⁵ He thought that air normally filled the arteries and attributed apoplexy to an accumulation of phlegm in the arteries of the brain. Around the time of Christ, Celsus, a Roman physician, distinguished between "apoplexy" - a paralysis of the whole body - and "paralysis" - in which the effects were localised. At the same time it was realised that the nervous pathways cross, such that a lesion on one side of the head caused signs on the other side of the body, and in late Roman times the term "hemiplegia" was first used.⁶

Understanding of cerebral function took a giant leap forward with the concept that blood circulated through the brain, and the recognition of the vascular interconnections of the circle of Willis. Willis (1621-1675) was not the first to describe this anastomosis of arteries at the base of the brain, but he was probably the first to recognise its

importance for collateral supply by describing a patient with occluded right carotid and vertebral arteries who did not suffer apoplexy or paralysis.^{6,7} Richard Lower (1631-1691) a colleague of Willis's demonstrated the ability of the Circle of Willis to maintain cerebral circulation even when three out of four supplying arteries were tied off.⁷

There followed a series of pathoanatomic studies of patients who had died of apoplexy, the most important being those of Johann Jakob Wepfer (1620-1695). He described intracerebral and subarachnoid haemorrhage, and developed the theory that obstruction of arterial inflow or venous outflow of the brain could cause apoplexy. He noted that carotid narrowing can result from "corpora fibrosa" (small fibrous bodies) in the arterial wall, and that this could reduce the blood supply to the brain. He found that apoplexy was commonest in the obese, those whose face and hands were livid, and those whose pulse was consistently irregular, this representing the first realisation that cardiac disease could predispose to stroke. He recognised that the brain could not withstand interruption of blood supply even for a short period of time, that clinical patterns of apoplexy were variable, and made the first attempt to correlate the variable clinical manifestations of stroke with underlying pathology.^{6,7}

Francois Bayle (1622-1709) was the first to relate carotid atheroma to apoplexy.^{6,7} William Heberden (1710-

1801) described TIA's and Carolus Linnaeus (1707-1778) described aphasia.^{6,7} Samuel Johnson (1709-1784) described experiencing a TIA.⁶ Virchow (1847) noted that embolism was a frequent cause of brain softening, although others before him had realised that arterial disease could be responsible for "softening of the brain".⁶ Burrows in 1846 produced evidence of a relationship between "cerebral accidents" and alterations in cerebral circulation either due to a fall in blood pressure or anaemia. He noted that cardiac and cerebral apoplectic symptoms could occur simultaneously. In his experiments he demonstrated that the amount of blood in the brain could vary, and that such variations could be responsible for clinical signs.⁸ The latter was a milestone in the understanding of cerebrovascular pathophysiology.

From the 1900's to the 1950's.

Around the turn of the century, increasing attention focussed on carotid atheroma and the heart as sources of embolism to the brain. Sir William Gowers (1885) described cerebral embolism as being the result of "a morbid process elsewhere in the ventricular system commonly the heart" and that thrombosis resulted from local atheromatous disease.⁹ In the late 1800's there were several descriptions of cases of embolism from the heart or "diseased and roughened arteries" supplying the brain, and that in a number of cases recovery was rapid and complete. Chiari (1905) emphasised

the frequency of atherosclerosis in the region of the carotid bifurcation, believing that such lesions caused cerebral symptoms from embolisation. He stressed the importance of examining the cervical portions of the carotid arteries of all patients dying of stroke, having been caught out himself by omitting to examine the carotids in a patient dying of embolic stroke.¹⁰

In 1906 Sir William Gowers wrote that "Most cases of softening of the brain are due to the arrest of the blood supply by occlusion of an artery.....The sudden obstruction of a large vessel, however produced, frequently entails a distinct apoplectic attack.... In atheromatous thrombosis, focal symptoms, especially hemiplegia, come on before coma", thus noting the frequent progression of symptoms following large cerebral artery occlusion.⁹

J Ramsay Hunt, in 1914, emphasised that strokes could be caused by extracranial occlusion of cerebral arteries, and described the syndrome of internal carotid occlusion, but unfortunately his work and that of Chiari and Gowers went largely unrecognised (in America at least) for the next forty years due to the habit of embalming bodies for which the undertaker required intact carotid arteries.⁶

In 1925 Dow¹¹ reported that the carotid bifurcation and siphon were sites of predilection for atheroma and occlusion. Hultquist in 1942 published the post mortem findings of the entire carotid system in 1400 autopsies. He

noted the location, pathogenesis, histology, and propagation of thromboembolism and resultant changes in the brain.¹² In the 1950s it was realised that carotid artery occlusion was probably far more frequent than had previously been recognised, and could occur without symptoms. Although the exact aetiology of carotid thrombosis was unknown at that time, the two most commonly associated factors were atherosclerosis and thromboangiitis obliterans. Fisher in 1951¹³ reported eight patients with internal carotid occlusion and emphasised the relationship between carotid occlusion in the neck and cerebrovascular insufficiency. He said that internal carotid artery disease might prove to be a major cause of stroke. Seven of his eight patients had prodromal TIAs. He re-emphasised that the relationship between internal carotid artery thrombosis and symptoms was a function of the adequacy of collateral arteries, and that thrombosis occurred secondary to atheroma. He also commented that "unexplained cerebral embolism may arise from thrombotic material lying in the carotid sinus". In 1954 he wrote "Mural thrombus deposited upon atheromatous ulceration within the carotid sinus is not infrequent, especially if smaller microscopic deposits are included. Small emboli must often break away without causing symptoms or even cerebral lesions.... It has not been possible to get a clear understanding of the manner in which such emboli arise. Slowing of the blood flow, turbulence, or mural deposits are among the possibilities.

In one case the embolic material was wholly composed of platelets".¹⁴

Thus the major concepts underlying cerebrovascular disease pathogenesis were established by careful pathological studies and shrewd clinical observation:

- that "strokes" may be due to cerebral haemorrhage or infarction;
- that cerebral infarcts are due to thrombotic or embolic cerebral artery occlusion and symptoms depend on the adequacy of collateral channels;
- that emboli may arise from the heart or atheroma in the neck;
- that major strokes may be preceded by warning TIA's;
- that the risk factors for stroke include increasing age, TIAs, cardiac disease and atheroma.

In the 1920s, the development of angiography allowing examination of the carotid arteries in the living patient, helped to refocus attention on carotid atheroma as a cause of stroke and renewed interest in stroke epidemiology. That, plus better surgical techniques offering the possibility of preventive treatment, lead in the 1950's to the beginnings of scientific stroke research laying the groundwork for our current understanding of stroke pathophysiology, epidemiology, and therapeutic approaches.

1.1.4 Modern epidemiological studies :

Since the 1950's clinical and experimental work and advances in neuroimaging have lead to better understanding of the cerebral circulation, of risk factors for stroke, of how to investigate stroke and of preventive measures. Although post mortem studies provide information on disease pathogenesis, good epidemiological studies are essential to provide information on true disease incidence, aetiology and outcome. Only in this way can the relative importance of each risk factor be assessed and accurate figures on natural history be generated.

There have been several surveys of the frequency of stroke. While clinical observation is a satisfactory method of diagnosing stroke in epidemiological studies, it is not sufficient to identify the type of stroke. For example it is not possible clinically to differentiate a cerebral infarct from an intracerebral haemorrhage.¹⁵ The distinction depends on Computed Tomographic (CT) or Magnetic Resonance (MRI) brain imaging or necropsy. Hospital based studies, and those which included all strokes (not just first ever strokes) are less reliable because they do not reflect the true incidence of stroke in the community. They are biased towards patients with more severe strokes or cerebral haemorrhage who are more likely to be admitted to hospital. At least 25% of stroke patients in the United Kingdom are probably not re-

ferred to hospital,²⁰ possibly a higher percentage in less developed countries. The most reliable epidemiological data come from the community based studies which looked at the incidence of first ever stroke, and used CT scanning (or post mortem) to diagnose the cause of stroke. There are six such studies now published: The Oxfordshire Community Stroke Project (OCSP),¹⁶ the SEPIVAC Study from Umbria, Italy,¹⁷ the Rochester study from Rochester Minnesota, USA,¹⁸ the Benghazi Study from Libya,¹⁹ the Shibata study from Japan,²¹ and the Hisayama study from Japan.²² The cause of stroke by pathological type as determined in each of these studies is shown in Figure 1.1.1. In the three Western and the Libyan studies, about 80% of first ever strokes were due to cerebral infarction, 10% to primary intracerebral haemorrhage (PICH), 5% to subarachnoid haemorrhage (SAH), and in 5% the cause was uncertain. The two Japanese studies suggested a higher incidence of primary intracerebral haemorrhage, but this could have been due to a lower CT scan rate and greater reliance on clinical findings than in the other four studies. Further evidence supporting these findings comes from a community-based study of cerebrovascular disease in Perth, Western Australia, which had a lower CT brain scanning rate (only 70%) but found that 88% of cerebrovascular disease was due to cerebral infarction (28% lacunar, 20% large artery occlusion) and 12% to cerebral haemorrhage including SAH.²³

Cerebral infarcts due to arterial occlusion may be

predominantly cortical (large or small) in the territory of a large or medium sized artery; lacunar in the deep white matter and basal ganglia (thought to be due to occlusion of a lenticulostriate artery²⁴); borderzone at the edges of adjacent large artery territories; or involve the cerebellum and brain stem in the vertebrobasilar artery territory. The clinical features and natural history of each of these types of infarction are different and should be taken into account in trials of new treatments and assessment of preventive measures.²⁵

The OCSF data were used to classify cerebral infarction into four clinical syndromes which might be used to predict the underlying cerebral arterial pathology and risk factors : Total Anterior Circulation Infarction (TACI) corresponding to large cortical infarcts; Partial Anterior Circulation Infarction (PACI) corresponding to small cortical infarcts; Lacunar Infarction (LACI); and Posterior Circulation Infarction (POCI) corresponding to cerebellar, brain stem and occipital lobe infarction.²⁵

A quarter of all patients with first ever cerebral infarction had lacunar infarction, 17% had TACI, 34% PACI, and 24% POCI. The clinical features of each syndrome are described in detail in Part 2 and Appendix Two. At one year, 11% of patients with lacunar infarction, 18% with a PACI, 19% with a POCI and 60% with a TACI were dead. Early recurrent stroke was most frequent following a PACI stroke. Late recurrent

stroke (in the first year) was most frequent following a POCI stroke. The one year outcome after first ever stroke in the OCSF is shown in Figure 1.1.2.

The common causes of large intracerebral artery occlusion are embolism from a source outside the head (large artery atheroma, cardiac or paradoxical embolism from the leg veins through a defect in the cardiac atrial septum, in situ thrombosis forming on an atheromatous plaque inside the head and propagation from thrombus in the carotid arteries in the neck. Rare causes of stroke include arteritis (temporal, Bect's disease, systemic lupus erythematosus, drug abuse, infective, granulomatous), moya moyo, etc, most of which tend to affect the small intracerebral arteries and are rare and outside the scope of this thesis.²⁶ In the Stroke Data Bank,²⁷ a hospital based study from America, 31% of cerebral infarcts were thought to be due to embolism (14% cardiac), 42% to large artery stenosis or occlusion, and the cause was uncertain in 29%. This study was biased towards large infarcts and probably misjudged the cause of mild strokes. In the OCSF community based study, analysis of the risk factors for the first 244 cases of first ever cerebral infarction showed that 20% had a cardiac source of embolism (13% were in atrial fibrillation), 38% had ischaemic heart disease, 52% were hypertensive, 14% had had TIAs, 14% had an arterial bruit in the neck, and 10% were diabetic ²⁸. Lacunar infarcts, or small subcortical infarcts are small in-

farcts in the deep white matter of the pons or cerebral hemispheres, or basal ganglia, and are due to occlusion of a single deep perforating artery. They probably arise by a different mechanism than cortical infarcts, possibly local atheroma at the origin of the perforating artery, or lipohyalinosis causing occlusion of the deep perforator, though there is considerable controversy surrounding this.²⁴ It is possible that small emboli are responsible for some lacunar strokes, although this is speculative.

1.1.5 The role of carotid atheroma as a cause of acute ischaemic stroke:

Atheroma in the carotid arteries (most commonly at the common carotid bifurcation though also not infrequently found at the common carotid artery origin) is a well established cause of stroke.^{29,30} One of the most important epidemiological points to emerge from the European⁴ and North American³¹ symptomatic carotid surgery trials was confirmation that carotid atheroma is a major cause of ischaemic stroke; the more atheroma and the tighter the stenosis, the greater the risk of stroke. If the cause (atheroma) was removed, the risk of stroke was greatly reduced. Patients with atheroma but stenosis less than 30% hardly ever had strokes, so non-stenosing atheromatous plaques carry a very low risk of stroke.⁴ The role of plaque ulceration (angiographically visible) as a separate risk factor to stenosis

has yet to be defined.

Despite the extensive literature which has accumulated on atheroma, there are still considerable gaps in our knowledge of atherogenesis.²⁹ "Fatty streak" - a macroscopic, flat, lipid-rich lesion consisting of macrophages and smooth muscle cells visible even in children - appears to be the earliest lesion of atheroma.²⁹ Later fibrous plaque - consisting of increased intimal smooth muscle cells surrounded by a connective tissue matrix containing variable amounts of intra- and extracellular lipid - appears. "Fatty streaks" and fibrous plaques tend to appear at similar sites in arteries lending weight to the precursor-product hypothesis. Both are most frequent in large arteries particularly at bifurcations and may in part be a "response to injury" of the arterial intima.^{29,32} There is also a complex interrelationship with plasma lipid concentrations, platelets, leukocytes and cell-derived mitogens well beyond the scope of this thesis. The tendency to develop atheroma may be familial and diet-related.

Established atheromatous lesions consist of a fibrous cap projecting into the arterial lumen, containing smooth muscle and macrophages, leukocytes and connective tissue. Beneath this there may be an area of necrotic debris, cholesterol crystals and calcification. Haemorrhage may occur into plaques causing acute increase in size and possible rupture, exposing the highly thrombogenic cholesterol mai-

trix to blood.^{33,34} Thrombus may form on the exposed surface reducing luminal diameter, and thrombus plus cholesterol-platelet debris may embolise downstream. Eventually the plaque may re-endothelialise becoming less thrombogenic and less active. Acute plaque rupture may result in acute occlusion even of large arteries like the internal carotid artery.^{34,40} This may be asymptomatic, or cause minor or major hemispheric stroke, depending on other factors like collateral blood supply to the hemisphere and distal propagation of the thrombus. Progression and regression of carotid atheroma has been demonstrated in patients using ultrasound.³⁵ In a few reported patients, even complete occlusion (angiographically) of the ICA has resolved⁴¹ so the dynamic nature of atheroma should not be overlooked.

The proposed cyclical behaviour of atheroma, with haemorrhage into the plaque, plaque rupture and increased thrombogenicity until the plaque surface has healed, may in part explain why the greatest risk of a completed stroke is within six weeks of a warning (TIA).⁴ It may also explain why some patients with carotid atheroma develop strokes and others with apparently similar lesions do not.^{36,37} Apart from the above, why some patients become symptomatic and others do not is unclear and presumably depends on a complex interaction of blood coagulation factors, flow dynamics, plaque constituents and surface properties, mechanical factors such as the shape of the carotid bulb, movement of

the neck and so forth.³⁷

Although carotid bifurcation atheromatous stenosis is a well established cause of stroke, it is only present in a large minority of patients with strokes and TIA's (45% and 36% respectively).³⁸ Other less common sites for atheroma in the arteries leading to the head are the origins of the common carotid arteries and the innominate artery, the carotid siphons and recently recognised as a possible cause of stroke, aortic arch atheroma.³⁹ In a recent autopsy series, ulcerated atheromatous plaques in the aortic arch were found in 16.9% of patients with cerebrovascular disease during life compared with 5.1% with other neurological diseases (odds ratio 4.0, $P < 0.001$). The prevalence of ulcerated aortic arch plaques was 61% among 28 patients with no known cause of cerebral infarction during life compared with 22% among the 155 patients with a known cause of cerebral infarction ($P < 0.001$). The presence of aortic arch ulcerated atheromatous plaques was not correlated with the presence of extracranial ICA stenosis, suggesting that the two were independent risk factors for stroke. The true role and interplay of atheroma at each of the above sites is uncertain, requiring further study to produce appropriate guidelines for patient investigation and clinical management.

1.1.6 Cardioembolic stroke

Emboli of cardiac origin probably account for about

twenty percent of cerebral ischaemic events.^{28,42} Thrombus forms in: the atrial appendage in patients with atrial fibrillation; on the ventricular endocardium following acute myocardial infarction; platelet fibrin thrombi may form on defective heart valves; or infective vegetations on the valves in infective endocarditis.^{42,43} Rarely atrial myxoma may embolise to the cerebral circulation, and embolic stroke may occur as a complication of coronary artery bypass surgery.⁴⁴

Recently, with improved non-invasive methods of cardiac imaging, the importance of atrial septal deformities has been recognised.⁴⁵ Atrial septal defects may allow paradoxical embolism of thrombus from the leg or pelvic veins to the arterial circulation,^{46,47} and atrial septal "aneurysm" defects (without a true communication between venous and arterial sides) may allow stasis of blood leading to thrombosis and embolism in the arterial circulation.⁴⁸ Post mortem studies of "normal" hearts have shown patent foramen ovale in approximately one third of persons aged between one and 29 years, and in about 25% of those aged over 80 years.⁴⁶ Fifty-five percent of young patients with unexplained ischaemic stroke were found to have a patent foramen ovale compared with ten to fifteen percent of controls (using transthoracic echocardiography).⁴⁶ Transoesophageal echocardiography is more sensitive than transthoracic, though so far less available, but is likely to lead to

improved understanding of the role of cardiac defects in stroke. Elevation of right heart pressure by even simple Valsalva-inducing activities such as coughing may reverse the normal left-to-right pressure gradient and allow paradoxical embolism to occur.

It is not infrequent to find more than one potential cause of stroke when investigating patients with cerebrovascular disease.^{27,28} It may be difficult to decide which potential cause was most likely responsible for the stroke, but with secondary preventive treatments becoming more clearly defined, it is increasingly important to ensure accurate identification of the balance of risk factors (see section 1.1.8). There may be differences in the type of stroke caused by emboli from a cardiac as opposed to a carotid source,^{42,49} but the reported differences vary with the study and may be the result of selection bias. Haemorrhagic infarction which was for some years regarded as a hallmark of cardioembolic stroke, is probably not simply due to the cardiac source but rather a function of infarct size (see section 1.1.7).

1.1.7 Current understanding of the sequence of events in the ischaemic brain following cerebral arterial occlusion

The brain requires a steady supply of blood to provide substrates for energy metabolism and to carry away waste products.⁵⁰ When blood flow is decreased below certain levels and substrate supply becomes insufficient, neuronal function fails.^{50,51} Most of the information concerning neuronal ischaemic thresholds has been derived from animal experiments. There is relatively little information from stroke patients due to (until recently) lack of non-invasive investigative techniques and methodological difficulties in getting patients quickly for study in the acute phase. In the 1970's experimental studies used electrophysiology and histology,^{51,52,53} but recently research has been directed more toward determination of biochemical markers of reversible and irreversible ischaemic damage. A relatively brief discussion of the likely sequence of events in the brain distal to an acute arterial occlusion will be given here, as a much more detailed description will be given in Part One, Chapter Six (on CT scanning) and in Part Three, Chapter One.

Experimental work on ischaemic thresholds in the brain has demonstrated two critical levels of decreased perfusion : first a level representing the flow threshold for reversible neuronal damage; and second a lower threshold below which irreversible neuronal membrane failure and morphological damage occur. The range of perfusion values

between these limits has been called the "ischaemic penumbra" characterised by the potential for functional recovery without morphological damage provided that local blood flow can be reestablished at a sufficient level and within a certain time window.⁵¹ The flow thresholds for reversible and irreversible ischaemia are remarkably similar in a variety of mammals including rats, cats, and baboons, and there is reasonable evidence that these flow thresholds will be similar in humans.⁵⁴ The ischaemic tolerance of neurones varies in different parts of the brain.⁵⁰ It is the combination of duration as well as the depth of ischaemia which determines the development of irreversible damage.^{50,51} Mild flow reduction may be tolerated for hours while profound flow reduction may cause neuronal death in minutes. As well as the varying neuronal tolerance to ischaemia, individual animals of the same species vary in their ability to withstand apparently similar ischaemic insults.⁵⁰ For example Hossmann et al repeatedly demonstrated that even one hour of complete cessation of blood flow to the brain can be followed by recovery of electrophysiological function and also by survival and recovery of neurological function in some animals.^{55,56} Similar results have been obtained with some focal cerebral ischaemia models (MCA occlusion), some animals dying early of the cerebral infarct and others making a good neurological recovery.⁵² Recent studies on acute stroke patients using positron emission tomography have clearly

suggested that the ischaemic but viable brain may survive for up to 48 hours after the onset of ischaemia in some patients.⁵⁴ This selective tolerance is likely to be due to a number of factors, the main one being the adequacy of the collateral circulation, but possibly also the metabolic state of the animal at the time of onset of ischaemia may be important. Presumably similar variability occurs in humans and in part explains the variable response of stroke patients to apparently similar vascular lesions, tolerance of the stroke, and degree of functional recovery.

It is important to stress that cerebral ischaemia is a dynamic process evolving in time and space within the brain, dependent on fluctuations in local blood flow, neuronal vulnerability and the effect of toxic metabolites released from damaged cells on this dynamic process. In addition, neurones with normal blood flow but connected to acutely ischaemic neurones (for example in the cortex overlying ischaemic white matter in the MCA territory) lose their evoked potential demonstrating an ischaemic effect on afferent pathways in the white matter.⁵⁰ White matter can tolerate longer periods of ischaemia than cortex so functional impairment due to deafferentation may have a better prognosis than cortical damage caused by direct cortical ischaemia. Bearing all this in mind, when faced with an individual stroke patient in the acute phase it is quite clear that it is not possible to judge how much brain is

permanently damaged, and how much reversible ischaemia is present just by examining the patient clinically. The hemiparesis could be due to shutdown of still viable neurones or equally to permanently damaged neurones.

Most animal experiments used a relatively artificial model to produce the ischaemic lesion.⁵⁷ Focal ischaemia models are probably more relevant to stroke patients than global ischaemia models, but even in the former sampling of the ischaemic tissue may be from only a relatively small selected area of the total brain, and it is difficult to extrapolate from that firstly to the whole animal, and secondly from there to humans, especially elderly humans. The usefulness of animal models has been questioned, but so far there has been little alternative, so their limitations must be constantly considered.⁵⁷

The response of ischaemic brain to reperfusion is unclear. There is some evidence from animal work that it may be beneficial in salvaging some of the ischaemic penumbra,⁵⁰ but there is also evidence that reperfusion may trigger a disastrous process of progressive neuronal injury due to a cascade of biochemical events started during the ischaemia.^{50,58} Severe changes in ion homeostasis, accumulation of lactate and release of free radicals and excitatory toxins may all contribute to this relentless process of neuronal death. There are anecdotal reports of patients who, following a severe ischaemic insult, make an apparently good

early recovery only to die a few days or weeks later of progressive brain damage.⁵⁸ The role of this toxic process in acute stroke is unclear, but could potentially limit any benefit that might result from early reperfusion and salvage of ischaemic penumbra. However the risk/benefit ratio of reperfusion of ischaemic tissue for stroke patients will only be established in the context of large randomised controlled clinical trials.

It has also been suggested that reperfusion of ischaemic or infarcted brain may worsen swelling of the infarcted tissue and increase the risk of haemorrhagic transformation of the infarct.^{52,59} In fact it has been said that the major cause of haemorrhagic transformation is reperfusion.⁵⁹ Again, the true role of reperfusion is unclear, there being also evidence from animal work⁶⁰ and stroke patients that reperfusion is not the cause of haemorrhagic transformation.^{61,62} Haemorrhagic transformation will be discussed further in Part One, Chapter Six and infarct swelling in Part Three, Chapter One.

In conclusion, there is some evidence that some brain tissue distal to an acute arterial occlusion survives for a limited period, offering a therapeutic window in which to intervene to reduce the final amount of neuronal damage, but it is not clear whether reperfusion of the ischaemic brain will be beneficial or not.

1.1.8 Prevention of, and therapeutic options for, acute ischaemic stroke

In the developed world stroke is still the third commonest cause of death after heart disease and cancer, and leaves many more people disabled.² Despite a decline in the incidence of stroke in the 1970s and early 1980's,^{63,64} anticipated demographic changes suggest that stroke will not continue to decrease in frequency.⁶⁵ Preventive measures, and treatment for the stroke once it has occurred, are needed more than ever.

Improved understanding of stroke epidemiology has lead to treatment of risk factors (hypertension, hypercholesterolaemia, reduction in smoking), carotid endarterectomy for symptomatic carotid stenosis, and aspirin. Reduction of risk factors may partly account for the decline in the incidence of stroke observed in the USA in the 1980's.^{63,64} The UK TIA Aspirin Trial showed that aspirin reduces the odds of suffering a major stroke, myocardial infarction or vascular death after a TIA by 15%,³ confirmed in the overview of antithrombotic treatment performed by the Antiplatelet Trialists Collaboration.⁶⁶ Aspirin is now a well established widely used preventive treatment for ischaemic stroke and other vascular disease, although the optimal dose is still controversial. The Dutch TIA Trial suggested that a dose of 30mg daily was as good as 300mg in preventing stroke, but caused fewer adverse effects.⁶⁷

Carotid endarterectomy was an established and commonly performed but unproven preventive treatment for patients with TIAs until 1991, when the interim results of the European Carotid Endarterectomy Trial (ECST)⁴ and the North Americal Symptomatic Carotid Endarterectomy Trial (NASCET)³¹ were published. Both showed that patients with 70% or greater stenosis of the symptomatic internal carotid artery benefited more from surgery than best medical therapy alone, even allowing for the risk of surgery. Patients with less than 30% stenosis had virtually no strokes so the risk of surgery was not justified. Both trials are continuing to randomise patients with 30 to 69% stenosis because the risk/benefit ratio of surgery in that group is not yet clear.

Therapeutic approaches so far tested for the treatment of acute ischaemic stroke once it has occurred, include haemodilution, antithrombotic drugs, thrombolytics, neuronal protective agents (ion channel modulators) and free radical scavengers. Haemodilution does not work in the generality of acute ischaemic stroke.⁶⁸ Antithrombotic drugs have been used in acute ischaemic stroke for many years but without definite evidence of benefit.⁶⁹ A large trial of aspirin and heparin in acute ischaemic stroke has just started in the UK and is extending to Europe and Asia (The International Stroke Trial). There are many ion channel modulators which have shown promise in experimental studies,⁷⁰ but so far

none have been beneficial in stroke patients.⁷¹ Many such drugs are currently under trial but often are found to have unacceptable adverse effects. Thrombolysis is promising but unproven and will be discussed in detail in Part 4.

The following chapters will describe investigative techniques for acute ischaemic stroke, their contribution to the improved understanding of stroke, and how they may be used to guide therapy.

Summary of Chapter One

1. A brief historical review discusses how clinical observation and pathological studies up to the 1900s provided fundamental information on the aetiology and pathogenesis of acute stroke.
2. Community based epidemiological studies have established the true incidence of stroke and shown similar frequencies for cerebral infarction and primary intracerebral haemorrhage in all parts of the Western World.
3. Carotid atheroma is the major cause of acute ischaemic stroke. The tighter the stenosis the greater the risk of stroke. Non-stenosing atheroma, even if ulcerated, carries a low risk of stroke.
4. The other common causes of stroke are emboli of cardiac origin, paradoxical emboli from the venous side of the circulation, atheroma in the aortic arch, and small arterial disease causing lacunar stroke.
5. It is likely that some neurones distal to an acute cerebral arterial occlusion survive in a shut down but viable state for a variable period of time, and are potentially salvageable, but it is not clear whether reperfusion is beneficial or may be associated with worsening of cerebral infarct oedema and haemorrhagic transformation.
6. Stroke is the third commonest cause of death in the Western World and is likely to remain so. It places an enormous burden on health care resources. It is important to

find an effective treatment.

7. Aspirin and carotid endarterectomy are now proven preventive treatments for acute ischaemic stroke.

8. There is no treatment of proven benefit for acute ischaemic stroke once it has occurred, despite intensive research efforts. Some promising treatments are under trial.

Cause of First Stroke by Pathological Type in Community Studies

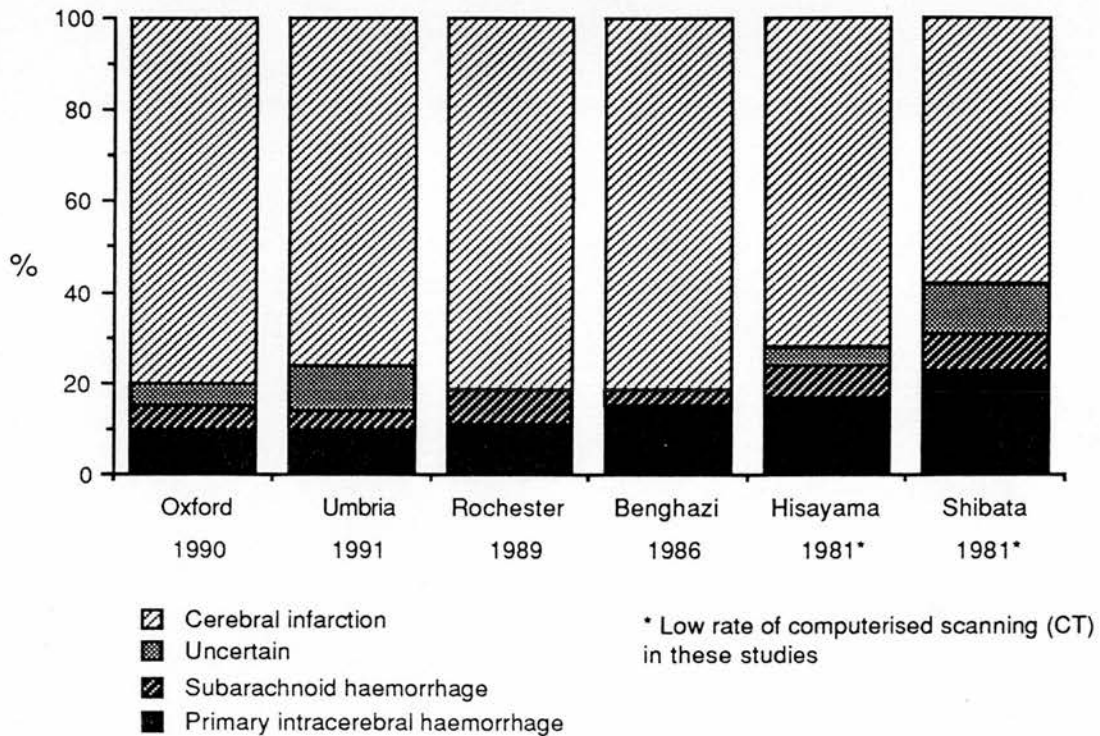


Figure 1.1.1 Cause of First Stroke by Pathological Type in the Community Based Studies. Oxford 1990 = The Oxfordshire Community Stroke Project (16), Umbria = SEPIVAC (17), Rochester = The Rochester, Minnesota Study (18), Benghazi = Benghazi, Libya (19), Hisayama = Japan (22), Shibata = Japan (21). The Figure was prepared by Dr R Lindley.

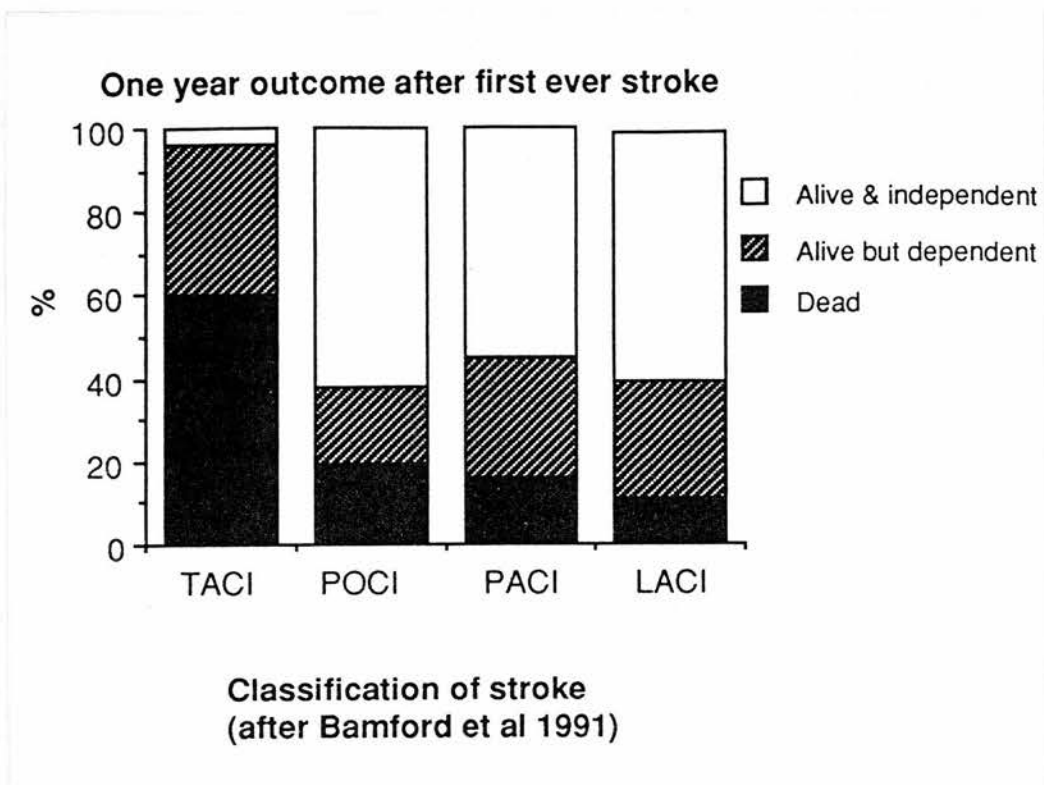


Figure 1.1.2 Outcome at One Year After First Ever Stroke (Cerebral Infarction) by Clinical Classification Data from the Oxfordshire Community Stroke Project (16): TACI = total anterior circulation infarction, POCI = posterior circulation infarction, PACI = partial anterior circulation infarction, LACI = lacunar infarction. The clinical classification is defined in Appendix Two. The Figure was prepared by Dr R Lindley.

Part One

Chapter Two

A Brief Outline of Normal Cerebrovascular Anatomy and Control of Cerebral Blood Flow.

- 1.2.1 Anatomy of the cerebral circulation
 - 1.2.2 The internal carotid artery
 - 1.2.3 The middle cerebral artery
 - 1.2.4 The anterior cerebral artery
 - 1.2.5 The posterior cerebral artery
 - 1.2.6 The collateral pathways : intracranial, and
intracranial to extracranial pathways
 - 1.2.7 The physiology of cerebral blood flow -
basic principles
 - 1.2.8 The control of cerebral blood flow
 - 1.2.9 Cerebral perfusion reserve
- Summary of Chapter

1.2.1 The anatomy of the cerebral circulation

The brain requires a constant flow of blood for supply of oxygen and glucose as well as other metabolic substrates and for removal of products of metabolism, so it has a good arterial blood supply. The two internal carotid arteries run anteriorly in the neck to supply the anterior part of the brain (frontal, parietal and part of the temporal lobes), and the two vertebral arteries run posteriorly in the vertebral canals of the cervical spine to supply the posterior part of the brain (brain stem and cerebellum, occipital and part of the temporal lobes).⁷² The internal carotid arteries (ICA) arise from the common carotid arteries (CCA) which in turn arise from the brachiocephalic trunk on the right and direct from the aortic arch on the left. The CCAs divide, usually at the level of C3/4 or C4/5 vertebral bodies, into the ICAs and external carotid arteries (ECA). The ECAs supply the extracranial tissues of the head and the dura. The ICAs enter the intracranial cavity through the foramina laceri and carotid canals in the skull base, branch and anastomose with the posterior circulation through the Circle of Willis. The two vertebral arteries (VA) enter the head through the foramen magnum and join to form the basilar artery (BA) which runs superiorly anterior to the brain stem, dividing at the level of the upper pons into the

two posterior cerebral arteries (PCA). The PCAs course posteriorly above the tentorium cerebelli to supply the occipital lobes, and also anastomose with the anterior cerebral circulation through the Circle of Willis. Figure 1.2.1a and b show the course of the carotid and vertebral arteries in the neck, and Figure 1.2.1c and d the main components of the Circle of Willis.

1.2.2 The Internal Carotid Artery (ICA):

The origin of the ICA has a fusiform widening (the carotid bulb or sinus). This is the commonest site for atheroma formation affecting the cranial circulation in caucasian populations.³² The purpose of the carotid bulb is unclear, but it may act as a filter point to trap debris, or to smooth arterial pulsations so that the brain is not exposed to violent pulsations. Usually no branches arise from the ICA until it enters the skull through the foramen lacerum, where it gives off small arteries to the dura. It then passes through the carotid canal to the cavernous sinus where it gives off small arteries to the dura around the pituitary gland. After leaving the cavernous sinus, the ICA enters the subarachnoid space, gives off the ophthalmic, posterior communicating and anterior choroidal arteries, and some small perforating arteries (to the basal ganglia), and terminates at the medial end of the Sylvian fissure by dividing into the middle and anterior cerebral arteries

(Figure 1.2.1b).⁷² The subarachnoid part of the ICA usually follows a tortuous course and is called the carotid siphon. The carotid siphon may also act as a physiological filter to catch debris before the blood enters the brain.⁷³

1.2.3 The Middle Cerebral Artery (MCA):

The first part of the MCA passes laterally in the Sylvian fissure (M1 segment). It measures between 18 and 26 mm in length, and is 2.5 to 4.9 mm wide at its origin (mean 3 mm).⁷⁴ Numerous small perforating arteries (lenticulostriate - LSA) arise from this segment at virtually 90 degrees to the M1 and pass superiorly into the brain substance to supply the basal ganglia and internal capsule (Figure 1.2.2). The LSA are end-arteries. Usually those arising medially are smaller than those arising from the lateral end of the M1, and a few may arise from the terminal ICA. The MCA bifurcates as it turns approximately 90 degrees to run superiorly and parasagittally in the Sylvian fissure (M2 segment). There are two large divisions in 78%, three large divisions in 12%, and a continuous main stem with no major divisions in 10% of subjects. In the commonest pattern (two large divisions), the anterosuperior division supplies the anterior part of the peripheral MCA territory, and the posteroinferior division supplies the temporal and posterior parietal parts. The branches pass through the Sylvian fissure to the external surface of the cerebral cortex of the

temporal, parietal and posterior parts of the frontal lobes. Perforating end-branches pass down into the cortex to supply the brain parenchyma. The territory supplied by the MCA is shown in Figure 1.2.3.

1.2.4 The Anterior Cerebral Artery (ACA) :

The ACA arises from the terminal ICA and runs anteromedially inferior to the frontal lobes (A1 segment).⁷² Small perforating branches supply the septal region, hypothalamus, and a larger branch, the recurrent artery of Hubner, supplies the caudate nucleus, anterior part of internal capsule and anterior third of the putamen. The anterior communicating artery (Ant Co A) links the two ACAs just anterior to the optic chiasm forming the anterior anastomosis of the Circle of Willis. There is considerable variation in the size of the A1 segments and the Ant Co A, illustrated in Figure 1.2.1c. The ACAs continue in an anterior direction (A2 segments) for a short distance, then turn superiorly into the interhemispheric fissure external to the corpus callosum. The A2 segments divide into the pericallosal and callosomarginal arteries, and perforating branches of these supply the cortex of the frontal lobes and medial parts of the parietal lobes (see Figure 1.2.3).

1.2.5 Posterior Cerebral Arteries (PCA) :

These are formed by the bifurcation of the basilar artery. They run posterolaterally around the midbrain, medial to the hippocampus, inferior to the optic tract, to pass over the free edge of the tentorium and thence to supply the inferior surface of the temporal lobes and the occipital lobes.⁷² The posterior communicating arteries (Post Co A) run anteriorly from the PCAs to join the ICA siphon and complete the Circle of Willis. Branches of the PCA supply the thalamus, the brainstem, choroid plexus and walls of the lateral and third ventricles (Figure 1.2.3). The posterior circulation anatomy is very variable. Frequently the main supply to the PCA is from the carotid arteries via the Post Co A, with only a vestigial supply from the basilar artery (see Figure 1.2.1c).

1.2.6 The collateral pathways : intracranial and intracranial to extracranial pathways :

The main intracranial anastomosis is provided by the Circle of Willis and its twenty-one common variations are shown in Figure 1.2.1c and d.⁷⁵ In most subjects the Circle of Willis ensures adequate supply to all parts of the brain, but some individuals may be at risk of impaired cerebral circulation should a major neck artery stenose or occlude as their Circle is incomplete. The anterior part of the Circle provides poor collateral supply in 24% and no collateral

supply in 7% of subjects studied at post mortem.⁷⁵ Note also that with age, atheroma may stenose or occlude some components of the Circle reducing its collateral function. Tumours, emboli, aneurysms, trauma and surgery may also cause interruption of part of the Circle of Willis. Anastomoses also exist between the pial branches of the major intracranial arteries linking their territories though these also vary in their adequacy.

In addition to the Circle of Willis, there are numerous potential collateral sources linking the extracranial to the intracranial arteries which open up when the blood supply via the ICA or VA becomes impaired.⁷⁶ The ophthalmic artery is the largest and flow may be reversed through it when the ICA is tightly stenosed or occluded. Potential anastomoses also exist between :

- the maxillary artery (anterior tympanic branch), ascending pharyngeal artery and the posterior auricular artery (stylo-mastoid branch) with the ICA dural branches in the carotid canal - carotico-tympanic anastomosis;
- the internal maxillary artery to the pterygoid branch of the ICA;
- the middle meningeal artery to the cavernous (dural) branches of the ICA.

The ECA also anastomoses with the muscular branches of the VA. The VA also anastomoses with the muscular branches of the subclavian arteries (thyrocervical trunk) and may

act as a collateral artery itself when the proximal subclavian artery is occluded, which if symptomatic is known as the subclavian steal syndrome.⁷⁶

A

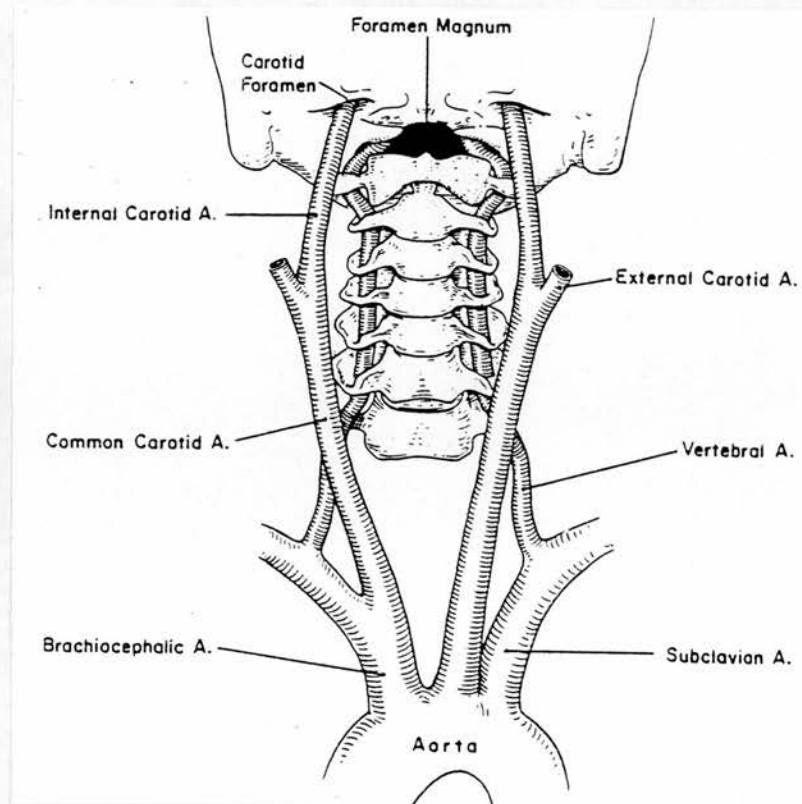


Figure 1.2.1 Anatomy of the Arteries to the Head and Brain.
A : Carotid and Vertebral Arteries in the Neck,
B : The Main Branches of the Internal Carotid Artery :
 a) meningo-hypophyseal trunk, b) artery of the inferior cavernous sinus, c) capsular artery, d) ophthalmic artery, e) posterior communicating artery, f) anterior choroidal artery, ACA) anterior cerebral artery, MCA) middle cerebral artery.

B

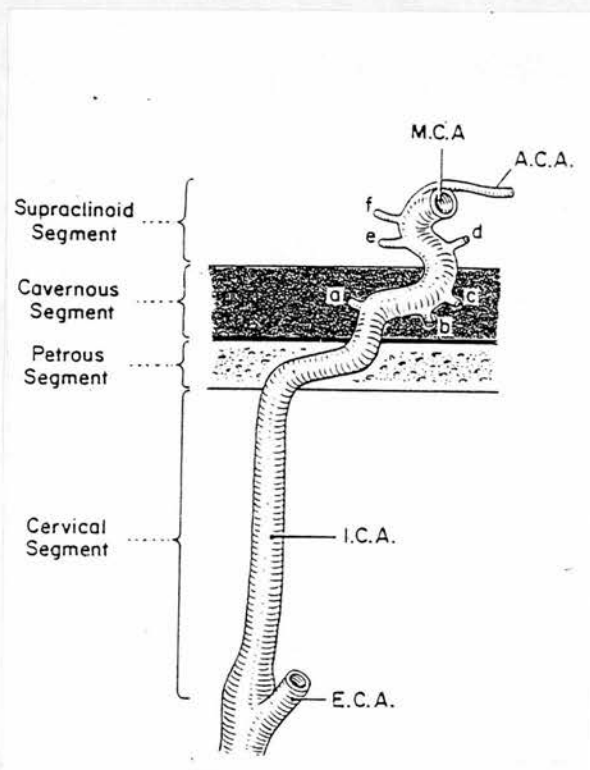
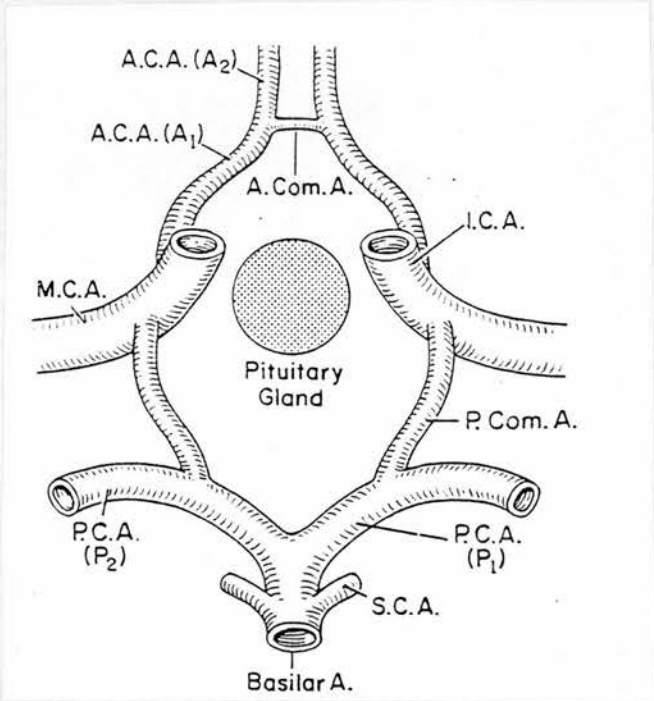
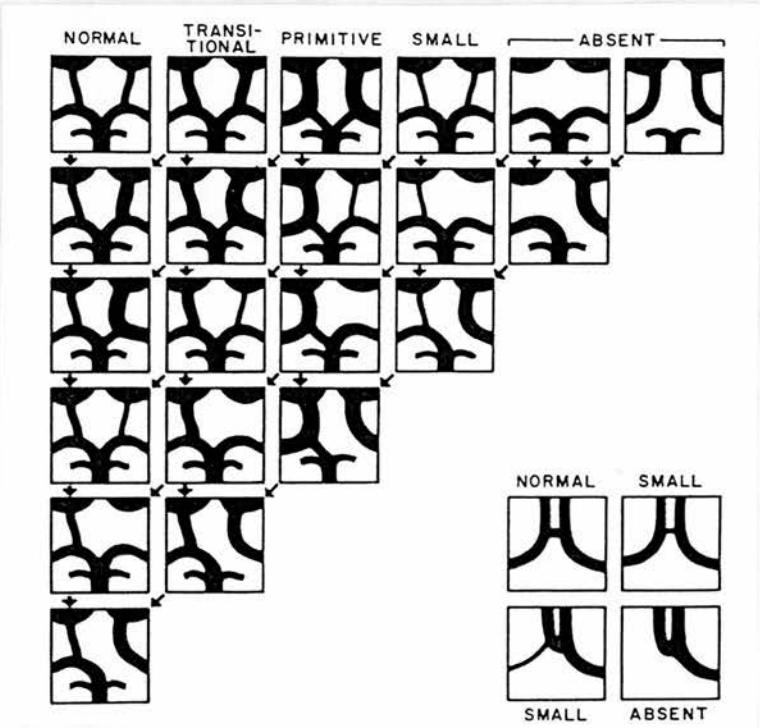


Figure 1.2.1 C : The Circle of Willis : PCA) posterior cerebral artery, P Com A) posterior communicating artery, A Com A) anterior communicating artery, SCA) superior cerebellar artery, other abbreviations as in B above.



D : Diagram illustrating the common variations of the Circle of Willis ; upper left are the 21 variations of the P Com A and its connections with the basilar artery ; lower right are four arrangements of the A Com A and ACAs.



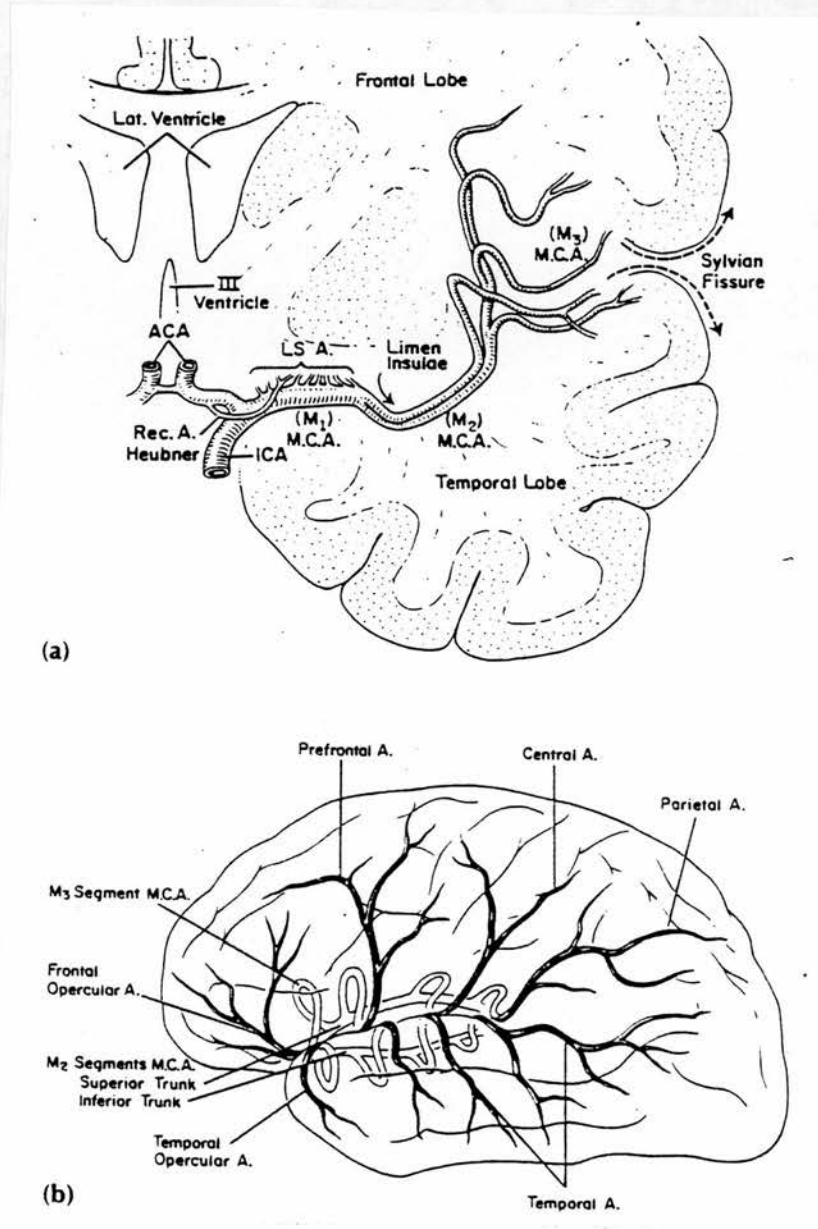
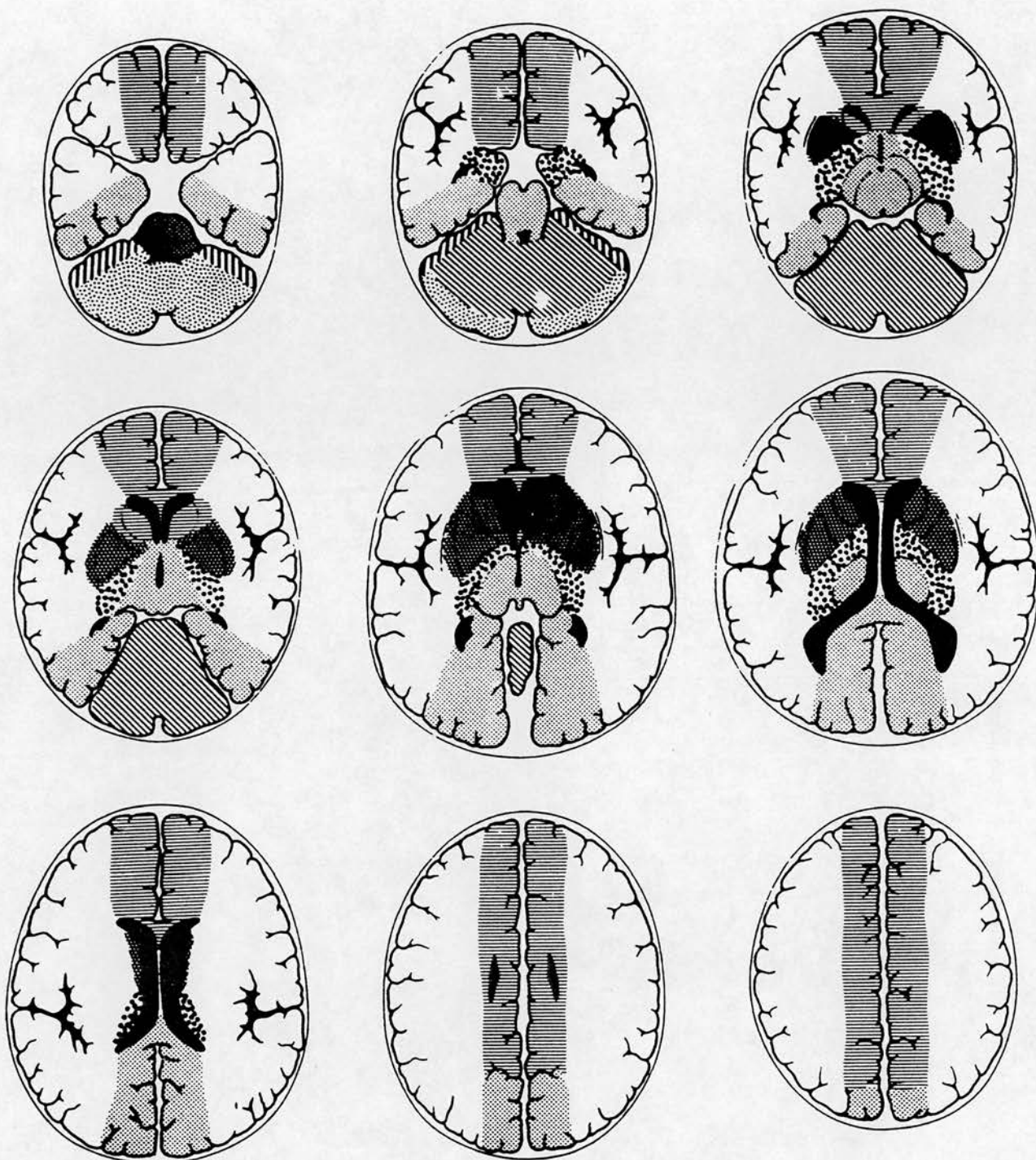


Figure 1.2.2 The Middle Cerebral Artery :

A) view in the coronal plane of the origin, main trunk (M1) and major branches (M2 and M3).

B) view of the lateral aspect of the cerebrum showing the MCA branches emerging from the Sylvian Fissure to supply the parietal, temporal and posterior parts of the frontal lobes (white vessels are the MCA branches within the Sylvian Fissure and black vessels have left the Fissure and are running on the surface of the brain).



 PICA
 BA
 AICA

 SCA
 PCA
 AChA

 ACA
 MCA
 LSA

Figure 1.2.3 The Vascular Territories of the Major Cerebral Arteries. PICA = posterior inferior cerebellar artery, BA = basilar artery, AICA = anterior inferior cerebellar artery, SCA = superior cerebellar artery, PCA = posterior cerebral artery, A Ch A = anterior choroidal artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, LSA = lenticulo-striate arteries. (72)

1.2.2 The physiology of cerebral blood flow - basic principals

The control of cerebral blood flow (CBF) is very complex. The brain is unique in exerting control over its own blood flow to ensure a constant supply of glucose and oxygen. Blood flow can be modelled on fluid flowing in a rigid system of tubes, where

$$\text{Flow} = \text{Pressure} / \text{Resistance} \quad (1)$$

Resistance is proportional to the diameter and length of the tube, and the viscosity of the fluid :

$$\text{Resistance} = 8 \cdot n \cdot l / \pi \cdot r^4 \quad (2)$$

where n = viscosity of the fluid

l = length of the tube

π = pi

r = radius of the tube

The flow of fluids, that behave with Newtonian characteristics, through rigid tubes in a laminar fashion is described by the Hagen-Poiseuille Law, which takes into account the pressure gradient across the tube, the tube length and radius and the fluid viscosity :

$$F = dP \cdot \pi \cdot r^4 / 8 \cdot n \cdot l \quad (3)$$

where F = volume flow

dP = pressure difference between the beginning
and end of the tube

π = pi

r = radius of the tube

n = viscosity of the fluid

l = length of the tube

However the circulation of blood in the body behaves rather differently. Blood is non-Newtonian (that is blood viscosity varies inversely with shear rates, the lower the shear rate the higher the viscosity), the perfusing pressure is pulsatile, the tubes are not rigid but have elastic recoil, the length and diameter of the blood vessels varies, but flow for the most part is laminar except at bifurcations. Generally speaking, for practical purposes, it is accepted that the Hagen-Poiseuille Law adequately describes the cerebral circulation for arteries larger than 100 microns in diameter at least.⁷⁷ In normal conditions in healthy brain the pressure gradient and radius of the conductance arteries (diameter greater than 100 microns) are the major determinants of blood flow, but in areas of focal cerebral ischaemia where the arterioles are already maximally dilated and autoregulation (see below) is impaired, blood viscosity becomes an very important determinant of blood flow.⁷⁷ The most important factor influencing blood viscosity is haematocrit, particularly at low shear rates. Erythrocyte and platelet aggregation as might occur in brain ischaemia, also influence blood viscosity. In the cerebral microcirculation (blood vessels of 70 microns or less) blood viscosity decreases as blood flows through progressively smaller capillaries. This is probably due to a progressive reduction in

haematocrit as capillary diameter decreases down to 6 microns in diameter - the Fahraeus effect - and is partially responsible for the failure of the Hagen-Poiseuille Law to describe accurately cerebral blood flow.⁷⁸ The Fahraeus effect varies with the haematocrit of the incoming blood: at constant flow rates it is linearly proportional to the incoming haematocrit whereas at unsteady flow rates the effect is variable. In addition, in larger capillaries the Fahraeus effect is inversely proportional to the haematocrit but is independent of the haematocrit in smaller capillaries.⁷⁷ Other factors such as the mechanical properties of the capillaries and erythrocytes, the behaviour of the leucocytes and platelets both physiologically and pathologically influence the cerebral microcirculation but are beyond the scope of this introduction.

There are several terms which can be used to describe cerebral blood flow. They are not interchangeable. **Absolute flow** (or volume flow) is the volume of blood entering the brain or area of interest per unit time in millilitres per minute. **Perfusion** is the flow per unit weight of tissue per minute in millilitres per 100g of brain per minute. **Velocity flow** is the speed at which blood is flowing in centimetres per second and is independent of the volume flowing. Doppler ultrasound measures velocity flow. **Transit time** is the time taken for an amount of blood to go from one part of the circulation to another point in seconds.⁷⁹

As blood flow is pulsatile, velocity flow can be expressed as a peak or mean :

$$\text{mean velocity} = F/\pi.r^2 \quad (4)$$

where mean velocity = mean velocity of flow (cm/s)

F = volume flow mls/s

$\pi = \pi$

r = radius of the vessel.

Substituting in equation (3) :

$$\text{mean } v = dP.r^2 / 8.n.l \quad (5)$$

Thus volume (or absolute) flow is proportional to the fourth power of the radius, and velocity flow is proportional to the second power of the radius, whereas all other factors (dP, n, and l) affect velocity and volume flow in a linear manner.

The cerebral circulation is also influenced by resistance to flow, compliance, and intracranial pressure. The main site of resistance is the smaller pial arteries (66% of pressure drop) and most of the rest occurs in the larger pial arteries (33%), but overall resistance in the cerebral circulation is low so flow is high during diastole.⁸⁰

The cerebral arteries are very compliant which also increases the diastolic flow. The cerebral arteries become stiffer with age, so less compliant, and this contributes to the slight decline in CBF which occurs with increasing age.⁸¹

The influence of haematocrit on CBF is complex. The

main effect of haematocrit is through its effect on blood viscosity which increases exponentially as haematocrit rises.⁷⁹ The largest changes in blood viscosity with haematocrit occur in the physiologic range of haematocrit : for example a rise in haematocrit from 30 to 50 trebles blood viscosity.⁷⁷ An increase in haematocrit increases the oxygen carrying capacity of the blood so CBF falls. Reduced flow in turn raises viscosity further, and a vicious cycle may result until stasis occurs.⁷⁹ The normal cerebral circulation may compensate for blood viscosity increases by vasodilating to overcome the associated increase in cerebrovascular resistance. Patients with chronic obstructive airways disease have a raised haematocrit secondary to chronic hypoxia but their CBF is usually normal.⁷⁹ In addition viscosity autoregulation is independant of metabolic reactivity to oxygen, as the effects of changes in arterial oxygen content can be dissociated from changes in blood viscosity in patients with paraproteinaemia in which a high viscosity is accompanied by anaemia and CBF is normal.⁸² Blood viscosity is also influenced by red blood cell pliability which varies with pH and pO₂, a fall in pH or pO₂ increasing red blood cell stiffness and blood viscosity and decreasing CBF.⁷⁹

Intracranial pressure (ICP) is the other influence on CBF. Cerebral perfusion pressure is the difference between the mean arterial blood pressure and the pressure in the

veins in the subarachnoid space prior to entering the venous sinuses. If ICP should increase above the venous pressure the veins would collapse and flow cease, but the venous pressure tends to increase with rising ICP, and flow stops when the ICP approaches arterial pressures.⁷⁹

1.2.8 Control of cerebral blood flow

The brain does not store energy in any form, so it is dependant on a constant supply of glucose and oxygen and therefore blood flow, to sustain its high metabolic rate. Control of CBF is brought about through several different mechanisms : autoregulation, metabolic, chemical and neuro-genic regulation all working to maintain as constant as possible a blood supply to the brain in spite of changing conditions elsewhere in the body.

Autoregulation is the maintenance of constant CBF over a wide range of mean systemic blood pressures (50 to 130 mm Hg). Constant flow despite an increase in perfusion pressure implies an increase in vascular resistance, and since neither the viscosity of the blood nor the length of the cerebrovascular bed is likely to change in these rapid adjustments, this implies that as perfusion pressure increases there is a reduction in the calibre of the principal cerebral resistance vessels leading to increased resistance and no net change in CBF (Figure 1.2.4a).⁸³ A decrease in systemic blood pressure leads to dilatation of the resistance

arterioles and a fall in cerebrovascular resistance. Autoregulation probably takes place through alterations in smooth muscle tone in the small arterioles responding directly to blood pressure changes. If cerebral perfusion pressure falls below 40 mmHg the cerebral arterioles cannot dilate any further so the brain extracts more oxygen from the blood to compensate, and CBF is almost invariably reduced. Similarly when the perfusion pressure exceeds 140 mmHg, the cerebral arterioles are maximally vasoconstricted and CBF starts to increase.⁷⁹ Chronic hypertension shifts the autoregulatory response curve to the right, so that the upper and lower limits of autoregulation are at a higher systemic blood pressure than in normotensive subjects.⁸⁴ Sympathetic overactivity, such as occurs in response to trauma or stroke, increases the lower threshold of autoregulation so that cerebral ischaemia begins to occur when the perfusion pressure falls below 60 mmHg. Increased intracranial pressure with no change in systemic blood pressure reduces cerebral perfusion pressure and autoregulation similarly acts to maintain CBF. Autoregulation becomes impaired after a wide variety of systemic and cerebral insults including trauma, ischaemia, and around cerebral tumours and abscesses and may lead to a passive pressure-blood flow response. This is not always observed as sometimes in severely damaged brain, increases in arterial pressure after CBF has become reduced, may fail to induce



any increase in CBF. In these circumstances the patient is usually comatose and changes in arterial $p\text{CO}_2$ (see below) fail to produce the appropriate changes in CBF. Also although increases in arterial blood pressure fail to raise CBF, a fall in arterial pressure results in a sharp fall in CBF. The exact cause of this phenomenon of "false autoregulation" in severely damaged brain is not known but probably results from increased cerebrovascular resistance due to brain oedema or endovascular sludging.⁷⁹ Autoregulation may also be impaired above a carotid ligation so CBF tends to follow passively changes in mean arterial pressure (see below).⁸⁵

The cerebral arterioles are also very sensitive to changes in arterial CO_2 concentration, an increase in PaCO_2 causing vasodilatation and a decrease vasoconstriction.⁸⁶ CBF can change by 3% or more for each 0.13 kPa change in arterial CO_2 tension in the range 4.0 to 8.0 kPa. Even taking a few deep breaths can alter CBF so it is very important to take account of end tidal CO_2 (as an indirect measure of Pa CO_2) when measuring CBF (Figure 1.2.4b). The response to CO_2 is attenuated when the systemic blood pressure is lowered, and is impaired by physical insults such as trauma to the brain or ischaemia.⁸⁷ Hypoxia is a less potent CBF stimulator until the PaO_2 falls below 50 mm Hg.^{79,87}

CBF is also regulated by local factors such as a local increase in metabolic by-products leading to vasodila-

tation and increased flow.⁸⁷ Finally there are also **neuropeptides** and **prostaglandins** which alter cerebrovascular tone and CBF although these are less well understood.⁷⁹

Therefore the control of CBF can be thought of in terms of a complex set of interactions all responding to different influences, local or global, but all with the same aim - to maintain a constant or appropriate supply of oxygen and metabolic substrates to the brain. All these mechanisms are vulnerable, and are impaired, locally and globally, following brain damage.

1.2.9 Cerebral Perfusion Reserve (CPR)

Above a carotid ligation (or occlusion or tight stenosis), resting CBF may be maintained by vasodilatation of the cerebral arterioles, but the ability of the cerebral circulation to compensate further, for example for changes in PaCO_2 or blood pressure, is often impaired because the cerebral arterioles are already vasodilated and have only limited vasodilatory capacity left.⁸⁵ The amount of reserve vasodilatory capacity can be usefully expressed by the concept of **cerebral perfusion reserve (CPR)**. CPR is a measure of the amount by which the CBV increases for given falls in CBF, and is a very sensitive indicator of impaired cerebral perfusion. In other words, CPR is the ratio of the cerebral blood flow (or how much blood is still entering the area of brain per unit time) to the cerebral blood volume

(CBV - or how much the capillaries are already dilated in that area of brain), ie it is an index of how much reserve vasodilatory capacity is left in a given area of brain. If CBF remains constant and CBV increases, as might occur distal to a carotid stenosis in order to maintain a normal CBF, the CPR will be reduced and the ability of the cerebral circulation to compensate for further reductions in CBF also impaired.

If : $CBF \times \text{transit time} = CBV$

and : $CPR = CBF / CBV$

and : $\text{transit time} = CBV / CBF$

it therefore follows that :

$$CPR = CBF / CBV = 1 / \text{transit time}$$

This is a clinically useful concept, much more useful than a simple measure of either CBF or CBV in isolation, as it shows how much capacity is left to maintain the cerebral circulation in a given situation.⁸⁸ CPR may also usefully be thought of as an indicator of cerebral perfusion pressure.⁸⁹ Cerebral perfusion pressure is the difference between mean arterial blood pressure and the pressure in the cerebral venous sinuses. As cerebral perfusion pressure falls below a critical level, CPR will be reduced.

It is really only possible to measure CPR in patients accurately using positron emission tomography so it has been measured in a limited number of pathologies. CPR has been shown to indicate accurately impaired cerebral perfusion in

the cerebral hemisphere above a carotid occlusion in asymptomatic patients and in patients presenting with ipsilateral carotid territory stroke and TIA.⁸⁸ Note however that due to methodological difficulties in imaging acute ischaemic stroke patients, there is little published information on CPR in the acute stages of ischaemic stroke.⁵⁴ Studies with positron emission tomography have also shown (in a still limited number of patients) that once cerebral vasodilatation is maximal and CPR exhausted, metabolic reserve takes over keeping tissue alive to a certain point by increasing the oxygen extraction from blood.⁵⁴ Once metabolic reserve is exhausted also, the tissue starts to die.

As CPR is proportional to the inverse of transit time, it follows that cerebral transit time - which can be measured by simple isotope techniques - may also be a useful indicator of impaired cerebral perfusion. If CPR is reduced, cerebral transit time will be prolonged. It also follows that the transit time is proportional to the cerebral perfusion pressure. Methods of measuring cerebral transit time will be discussed in Part 1 Chapter 5.

Summary of Chapter Two

1. The anatomy of the arterial blood supply to the brain is described, including the territories supplied by the major intracranial arteries, the Circle of Willis, and other collateral pathways.
2. The physics of blood flow are described with respect to the cerebral circulation.
3. The physiological control of cerebral blood flow is described including autoregulation, and the influence of PaCO_2 , PaO_2 , and metabolites.
4. Different parameters of cerebral blood flow are defined.
5. The concept of cerebral perfusion reserve is discussed, its importance as a measure of impaired cerebral blood supply emphasised, and its relevance to the isotope mean cerebral transit time described in Part 1 Chapter 5, mentioned.

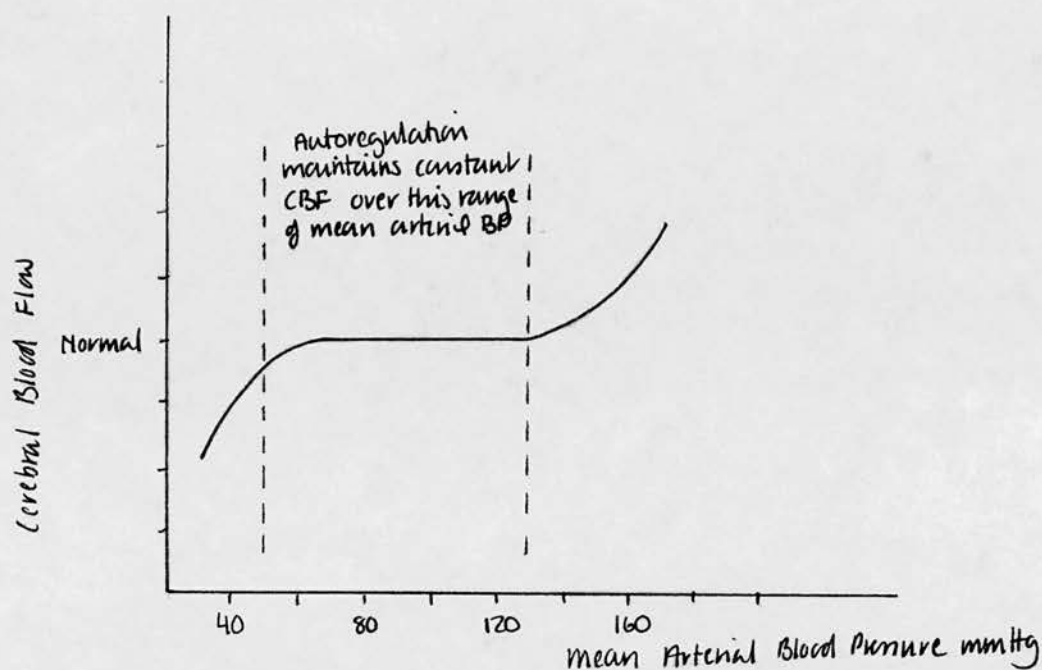


Figure 1.2.4 a The Effect of Systemic Blood Pressure on Cerebral Blood Flow - Autoregulation. (79,83)

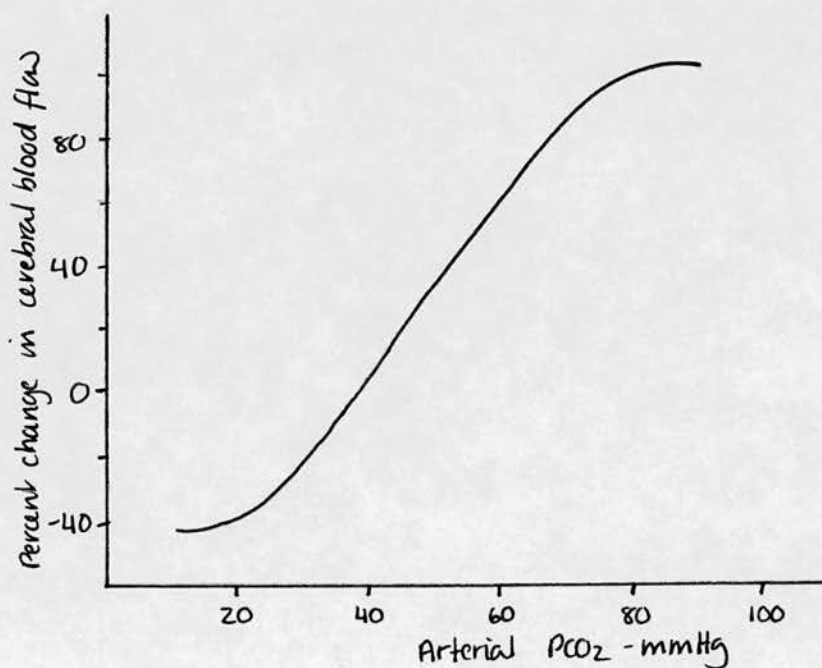


Figure 1.2.4 b The Effect of Change in PCO₂ on Cerebral Blood Flow. (79,86)

Preface to the chapters on imaging in cerebrovascular disease

Although experimental animal and pathological studies have laid the foundations for much of our understanding of stroke, more recently developments in Radiology have been crucial to the improved understanding of stroke epidemiology and pathophysiology, and made possible important therapeutic interventions.

There are several methods of imaging the brain. The intention of the rest of the introduction to this thesis is to describe the neuroimaging techniques relevant to stroke and outline the contribution each has made to improved understanding of stroke aetiology and pathophysiology. Cross-sectional imaging methods which show the brain parenchymal lesion are Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI). Prior to the development of CT scanning it was not even possible to differentiate reliably between intracerebral haemorrhage and cerebral infarction as the cause of stroke symptoms. The imaging methods which show the patency of the cerebral circulation are angiography, dynamic contrast enhanced CT scanning (of the basal intracranial arteries), and Magnetic Resonance Angiography. The first of these is invasive and not without risk but is still the only sure way of showing the cerebral arterial anatomy. Doppler ultrasound, simple isotope techniques using a gamma camera and "first pass" method, Single

Photon Emission Computed Tomography, and Positron Emission Tomography give information about blood flow patterns from which the patency or otherwise of the cerebral arteries can be inferred.

In acute ischaemic stroke, the two parameters of particular interest for clinical decision making are :

1. the nature of the brain parenchymal lesion manifesting as the stroke, and
2. occasionally the patency of the cerebral arteries.

There is no imaging technique yet available which gives the answers to both these questions, so a combination of imaging tests is required.

Each of the above techniques has contributed to improved understanding of the aetiology, pathogenesis, and natural history of acute ischaemic stroke. The development of modern ideas about acute ischaemic stroke is closely linked to information generated by each imaging technique. Therefore, each technique will be described in some detail to illustrate the contribution that neuroimaging has made to the understanding of cerebrovascular pathology, and to put in perspective the usefulness and practicality of simple non-invasive imaging tests in acute ischaemic stroke.

Part One

Chapter Three

Imaging of the Cerebral Vasculature in Cerebrovascular Disease - Invasive Methods :

Cerebral Angiography

1.3.1 Introduction and brief history of cerebral angiography

1.3.2 Risks of cerebral angiography

1.3.3 Angiography in cerebrovascular disease : the cervical
carotid and intracranial arteries

1.3.4 Concluding comments

Summary of Chapter Three

1.3.1 Introduction and brief history of cerebral angiography

X-rays were discovered in 1895, and the first attempt at angiography was in 1896 using a chalk containing solution injected into the arteries of an amputated arm.⁹⁰ Cerebral angiography was first attempted by Moniz in Lisbon, Portugal in 1927⁹⁰ by injecting sodium iodide as the contrast agent directly into the carotid artery following surgical exposure then taking a rapid series of skull x-rays to demonstrate the contrast medium in the cerebral circulation. The technique he used involved considerable risk from the sodium iodide and surgical exposure of the carotid artery. Further development of cerebral angiography was dependant on advances in contrast agents, needles, plastics for catheters and guidewires, and radiographic equipment.

Contrast agents have evolved through a series of increasingly safe ionic iodide solutions to the present day non-ionic contrast media, such as iohexol and iopamidol. Non-ionic contrast contains much more iodine per molecule of carrier so can be given in small amounts, typically 5ml of a solution containing 300mg of iodine per ml into the carotid artery, to achieve excellent visualisation of the intracranial arteries. General anaesthetic is no longer required, and allergic reactions, the main adverse effect of contrast media are rare with non-ionic contrast particularly when used intra-arterially.

Advances have also been made in catheterisation techniques. Direct puncture of the carotid or vertebral arteries using a hollow needle was superseded in 1953 by the technique devised by Seldinger in which a catheter could be inserted into a blood vessel over a flexible guidewire introduced through a hollow puncture needle after withdrawing the needle.⁹⁰ This permitted examination of all the cerebral vessels through one femoral arterial puncture in the groin. The first catheters used were difficult to manoeuvre so an important advance was the development of flexible, steerable guidewires and catheters. Catheters now have preshaped ends which aid positioning of the tip in the artery of choice. Angiography via the femoral artery route, has made cerebral angiography a much more practical technique. In the presence of severe bilateral aorto-iliac arterial disease precluding passage of a guidewire from femoral puncture to the aortic arch, it may still be necessary to examine the carotid arteries by direct puncture or by the brachial artery route retrogradely, but this is rare in practice.

Originally angiogram x-rays were acquired onto a series of rapidly exposed cut films at a rate of up to 4 per second over a period of up to 15 seconds depending on the rate of flow and whether venous as well as arterial images were required. Manual subtraction of the angiogram film from a masked film of the skull removed the bones leaving the

contrast-filled vascular structures more clearly visible but took up to twenty minutes per image. In the 1970's computerised x-ray image processing enabled electronic subtraction which now has virtually replaced cut film angiography for the cerebral and peripheral circulations. Known as digital subtraction angiography (DSA), the x-ray image is taken via the image intensifier into a digitised computer memory and may be instantly subtracted and played back, to yield angiographic images within a few seconds of the contrast injection. An added advantage is that smaller amounts of more dilute contrast medium may be used for intra-arterial injection, which may reduce the risk of the procedure without reducing image quality. The contrast may also be injected intravenously through a catheter with its tip near the superior vena cava to show the aortic arch and cervical portions of the carotid and vertebral arteries. Much larger volumes of contrast are required for this and quality of the images of the cervical and intracranial circulation is not usually sufficient for routine use.⁹¹

1.3.2. Risks of cerebral angiography.

The high risk of cerebral angiography when first introduced (from direct carotid puncture, toxic contrast agents and general anaesthetic) meant that it was initially used in the diagnosis of symptoms suggestive of cerebral tumours and not for cerebral vascular disease. It was felt

in the 1930's that as there was little that could be done about cerebrovascular disease, investigating it was meddlesome and dangerous.⁹⁰ However increasingly safe and practical techniques meant that cerebral angiography could be used more widely. As currently used, the risks of cerebral angiography are low but important. The risks are due to:

1) arterial puncture (dissection, disruption of plaque, gangrene possibly leading to amputation of the leg or death); 2) adverse reaction to the contrast agent; 3) damage to the carotid or vertebral artery intima by the catheter tip (dissection, displacement of atheroma or thrombus); and 4) careless injection of bubbles or particles into the cerebral circulation causing embolic stroke. The risk may be highest in patients with ischaemic cerebrovascular disease, who may have impaired cerebral circulation, more atheroma to displace, tortuous cervical arteries making catheterisation more difficult, and poor femoral arteries for access. Review of the eight prospective and seven retrospective studies from which it was possible to derive the complication rate of conventional cerebral angiography in patients with mild ischaemic cerebrovascular disease, showed a four percent risk of TIA or minor stroke, and a one percent risk of permanent neurological deficit.⁹² Mortality was less than 0.1%. Systemic complications were more frequent with intravenous DSA, mainly due to the large volume of contrast medium required. The complication rate was higher with inex-

perienced angiographers, with increasing duration of the procedure, and with increasing catheter manipulation. A prospective study of the complication rate of cerebral angiography in 200 consecutive patients with carotid ischaemi who had previously been screened with carotid Doppler ultrasound (to exclude those with normal or minimally diseased arteries) found neurological complications in 10% : 5% were TIAs, 1% were reversible and 6% were permanent neurological deficits, and 1% died from stroke as a direct result of cerebral angiography.⁹³ The incidence of angiographic complications was greater in patients with more than 90% stenosis and in those with persisting signs before angiography ($p<0.001$); it was also greater if performed by a senior registrar rather than a consultant ($p<0.005$).

Despite this, cerebral angiography is still the key and essential investigation in patients being considered for carotid endarterectomy, following subarachnoid haemorrhage, primary intracerebral haemorrhage, and to delineate tumour circulation, as it is the only method currently available of accurately showing the arterial pathology.

1.3.3 Angiography in ischaemic cerebrovascular disease

Angiography was the first means of examining the cerebral circulation during life in stroke patients. It enabled study of the cerebral arterial pathology soon after symptom onset and sequentially, rather than days or weeks later as with post mortem. Angiography has helped clarify several points of confusion which had arisen through pathological studies: 1) the apparent lack of a strong association between arterial occlusion and stroke; 2) stroke symptoms and the site of arterial occlusion; 3) that ICA occlusion is compatible with life and may be asymptomatic; 4) the importance of collateral arterial circulation; 5) the dynamic nature of cerebral arterial occlusion; and 6) it has helped to define aetiology for example the role of carotid atheroma. For all that, angiography has not been widely used in acute ischaemic stroke, as there was so little to offer the patient therapeutically. It has been more widely used as a prelude to carotid surgery.

The first report of ICA occlusion demonstrated by cerebral angiography was that of Sjoqvist in 1936.⁹⁰ In 1937 Moniz reported four cases of ICA occlusion in which the diagnosis was made by arteriography.⁹⁰ Advances in surgical and anaesthetic techniques combined with increasing understanding of the relationship between carotid atheroma and stroke encouraged vascular surgeons to operate on carotid arteries.¹²

In the early 1950's the first true attempts at carotid endarterectomy took place in France and in the United States preceeded by angiography to delineate the arterial lesions. Endarterectomy quickly became both controversial and popular.¹² The first objective attempt to assess the value of carotid endarterectomy, the Joint Study of Extracranial Arterial Occlusion, ran from 1959 until 1970 (total 6,535 patients) but random allocation to surgical or medical treatment only started in 1961. At that time surgical mortality was high and overshadowed the potential benefits.⁹⁴ However the data on 6,535 patients produced detailed demographic information, described arteriographic techniques, sites, and complications⁹⁵; delineated racial differences in the clinical and arteriographic manifestations of stroke; confirmed risk factors for stroke; reported frequency distribution and types of atherosclerotic lesions; and gave specific accounts of various sub-groups of patients, ie those having TIAs, subclavian steal syndrome, and ICA occlusion.⁹⁶

The boom in carotid artery surgery, continued until in the mid 1980's carotid endarterectomy was one of the most commonly performed operations in the United States and Canada.⁹⁷ Fortunately increasing scepticism about its benefit led investigators to start randomised trials of carotid endarterectomy for symptomatic carotid stenosis: the European Carotid Surgery Trial (ECST) began in 1981⁴; the United

States Veterans Administration Trial began in 1982; the North American Symptomatic Carotid Endarterectomy Trial (NASCET)³¹ began in the late 1980's and two trials of endarterectomy in asymptomatic patients are ongoing. Both the ECST and NASCET interim results showed that endarterectomy was better than best medical therapy alone in reducing the risk of stroke in patients with symptomatic carotid stenosis (> 70%) provided that the surgical morbidity was low. The best treatment for patients with less than 70% but greater than 30% stenosis is not yet known and both trials are continuing to randomise those patients.

Close analysis of the angiograms from patients entered in the ECST and NASCET trials will provide important data on different types of carotid lesion, their angiographic appearance and stroke risk. At present the association between plaque ulceration and the appearance of the lesion on angiography is known to be poor.^{36,37,98} The most important predictor of completed stroke is the degree of stenosis.^{4,36,37,98} The presence of ulceration (visible angiographically) has not yet been proven to increase stroke risk.

Despite all this it is still not possible to predict reliably which patients with ICA stenosis are at high risk of stroke.⁹⁹ Similarly it is not possible to predict reliably the patient's response to ICA occlusion, which may occur "silently" or be preceded by warning TIA's or precip-

itate minor or major hemispheric stroke. Spontaneous recanalisation of ICA occlusion has been documented by serial angiography in a few patients.⁴¹ It is unclear how often ICA occlusions recanalise, but it is probably infrequent. This is yet another example of the dynamic nature of the atherothrombotic process, being subject to the balance of thrombotic and antithrombotic agents in the blood and arterial wall, as well as pharmacological agents.

Relatively few studies have been done using angiography in the acute phase of ischaemic stroke, yet they have provided important information. Those in the 1950s and 1960s were more concerned with the extracranial cerebral circulation prior to endarterectomy. Several autopsy studies between 1920 and 1960 in patients dying after all severities of acute ischaemic stroke showed only one-half or less of all cerebral infarcts had a relevant arterial occlusion.¹⁰⁰ However, Adams and Fisher in a post mortem study of patients with recent large cerebral infarcts in 1961 found 90-95% were caused by thromboembolic occlusions.¹⁰¹ Jorgensen and Torvik¹⁰⁰ also found thromboembolic occlusion could be demonstrated in 89% of all recent (up to one and a half months) large infarcts at post mortem. In patients with small cortical infarcts, Winter and Gyori¹⁰² found thrombotic or embolic occlusion of the supplying artery in 16 of 21 cases. Part of the difficulty in demonstrating a relevant arterial occlusion, even in a recent infarct, at post mortem

may be due to rapid spontaneous lysis of the occluding thrombus. Small infarcts require meticulous dissection to identify the supplying artery and examine it for thrombus. Patients with cerebral infarcts, particularly those with small ones, tend to die weeks or even months after the event by which time the arterial pathology may have changed. Post mortem studies are also biased towards hospital-admitted patients who tend to have larger infarcts or intracerebral haemorrhage as the cause of symptoms. Patients with small infarcts (and less disability) may never be admitted to hospital²⁰ and are absent from many post mortem studies.¹⁰⁰

Angiography soon after symptom onset should give a more accurate indication of the number of ischaemic strokes due to embolic or thrombotic arterial occlusion. Early reports of angiography in acute ischaemic stroke suggested that it was fairly common to find normal looking arteries in the symptomatic territories.^{103,104,105} This may have been the result of : lysis of occluding thrombus; significant time delay between onset of symptoms and angiography; failure to differentiate cortical from lacunar and brainstem infarction (in the latter two, demonstration of an occluded perforating artery angiographically is virtually impossible, and small posterior fossa arterial occlusions may be difficult to identify also, giving the impression of normal arteries); failure to differentiate cerebral infarction from intracerebral haemorrhage (which would have been associated

with normal angiograms if small); or difficulty in identifying occlusion of small peripheral MCA branches due to tortuosity and overlap, and led to hypotheses such as arterial spasm or sudden falls in systemic blood pressure being the cause of the stroke rather than acute arterial occlusion. While thrombotic occlusion of the ICA in the neck was well recognised, it was increasingly suggested that atherosclerotic occlusive thrombosis in the MCA was quite rare,¹⁰⁶ particularly in persons of European origin. MCA stenosis has been reported in Western populations^{107,108} albeit less frequently than it is reported in persons of oriental origin.¹⁰⁹ Most of the post mortem and angiogram studies referred to in this chapter have assumed that it is possible to differentiate between in situ thrombosis, embolus, and stenosis by the appearance of the occlusion. This may not be correct. It should perhaps be remembered when reading the following that we do not really know how many intracerebral arterial occlusions are embolic (artery to artery, or cardio-embolic) and how many thrombotic.

In many of the early reports of cerebral infarction with no arterial occlusion at post mortem or angiography, there was evidence of a cardiac or arterial source of embolism.¹¹⁰⁻¹¹⁴ In fact the frequently normal intracranial circulation in patients with acute ischaemic stroke led to claims that the clinical diagnosis of embolism must have been wrong^{104,105} and that the stroke must have re-

sulted from hypotension or other transient cause of poor cerebral perfusion.

However there followed a series of reports of lysis and migration of emboli demonstrated on angiography. Gannon in 1962¹¹⁵ reported a patient with angiographically demonstrated occlusion of the MCA two weeks after symptom onset in whom a second angiogram two weeks later showed a normal MCA. Hollin and Silverstein in 1965¹¹⁶ reported four patients with angiographically demonstrated occlusion of the main trunk of the MCA within three days of symptom onset. On subsequent angiography or post mortem examination all were found to have patent MCAs. They pointed out that : the finding of a patent vessel after previous angiographically demonstrated occlusion cannot be used as definite evidence of a beneficial effect from thrombolytic or other therapies.

Zats et al in 1965¹¹⁷ reported four patients with MCA occlusions demonstrated by angiography within 24 hours of symptom onset in whom repeat angiography 24 hours later showed clearing of the occlusion with no underlying stenosis or vessel roughening. Two of the patients had received fibrinolysin but the other two had received placebo. Dalal et al in 1965¹¹⁸ described nine patients with acute ischaemic stroke and a cardiac source of embolism, in whom early angiography demonstrated appropriate MCA occlusion, which on follow up was found to have cleared. In some patients,

clearing of the occlusion was observed only minutes after the initial angiogram films, the lysis occurring spontaneously. Dalal went on to describe a prospective study of angiography in 26 consecutive patients with presumed cardio-embolic acute ischaemic stroke (their exact neurological findings were not stated).¹¹⁹ Twenty of the twenty-six patients had percutaneous cerebral angiography within six hours of the onset of symptoms, and seventeen had a second angiogram within a hundred hours of symptom onset. Twelve patients had MCA occlusion, four had ICA occlusion, one a PCA occlusion, and three patients had normal angiograms. On the second angiogram or post mortem (three patients), eight MCA occlusions had returned to normal, the occlusive lesion was unaltered in nine (including the ICA and PCA lesions), and the three normal angiograms were still normal.

Allcock in 1966¹²⁰ reported 40 patients with presumed cardio-embolic stroke due to MCA occlusion. All had angiography soon after symptom onset (exact timing not stated) and documented occlusion or severe stenosis of the MCA. Ten patients had repeat angiography : in five the previously occluded MCAs appeared normal; in three there had been some improvement in MCA patency; and in only two were the appearances unchanged.

Taveras et al in 1969¹²¹ found occluded intracranial arteries in 19 of 40 patients with acute presumed ischaemic stroke (time not stated). Only three patients had normal

cerebral arteries. The other 18 had capillary blush or early venous filling, or mass effect consistent with infarction (or a primary intracerebral haemorrhage) without occlusion of the territorial artery being demonstrated.

Fieschi and Bozzao in 1969¹²² reported 100 patients with clinical evidence of a "major" stroke in the previous 24 hours who had angiography within three days of symptom onset. Ten patients had presumed cerebral haemorrhage as the cause of stroke (clinical or post mortem diagnosis). Of the remaining diagnosed (most clinically and a few at post mortem) as ischaemic strokes, 57% had complete arterial occlusion in the neck or the intracranial ICA and its branches. In the remaining patients angiography showed localised or diffuse arterial stenosis without occlusion (site not stated). Repeat angiography or post mortem showed that the MCA had recanalised in eight patients and the distal ICA in two patients.

In more recent studies of acute ischaemic stroke, the angiography has been performed sooner after symptom onset. Solis and coworkers¹¹⁴ studied 104 consecutive patients admitted with acute stroke, and found appropriate cerebral arterial occlusions on angiography within 24 hours of symptom onset in 93% with a final diagnosis of ischaemic stroke (using CT scanning to exclude cerebral haemorrhage). Several studies have confirmed the high spontaneous lysis rate following intracerebral arterial, presumed embolic, occlu-

sion. Mohr et al in 1978¹²³ described cerebral angiography in 106 of the 215 patients with presumed cerebral embolism (cardio- or artery-to-artery embolus) studied in the Harvard Cooperative Stroke Registry, a hospital based study. In 88 patients with complete angiograms, 52 (60%) had arterial occlusion in the clinically affected territory and eleven of these had additional findings of stenosis, plaque or occlusion of the ipsilateral ICA. In the 36 (45%) patients without arterial occlusion, 22 (25%) showed atheromatous plaque in the ICA ipsilateral to the infarct, one had an early draining vein, one had an aneurysm, and twelve had normal angiograms. Seventy three percent of angiograms done within two days of stroke were positive for arterial occlusion, compared with only 28% performed after the second day. They also noted that there were no significant clinical differences between the 52 patients with arterial occlusion and the 36 patients without with respect to speed of onset, occurrence of coma, aphasia, seizures, infarction of any single cerebral lobe, clinical severity, or death in the hospital, and suggested that the lower incidence of arterial occlusion in the patients examined after 48 hours was due to spontaneous lysis of the occluding thrombus.

Olsen et al in 1985¹²⁴ reported a prospective study of consecutive acute ischaemic (CT confirmed) stroke patients below the age of 75 years admitted to hospital within three days of symptom onset. 40% had MCA occlusion, 12% had

ICA occlusion, 14% had severe ICA stenosis (of whom half were associated with MCA occlusion) and 41% were without significant MCA/ICA lesions (most of these were considered to be due to lacunes). This emphasised, with the Harvard Co-operative Stroke Registry, the importance of timing of angiography. Olsen et al had performed CT brain scans on all their patients and found that large infarcts on CT were always associated with MCA occlusion or a significant ICA lesion. In patients with medium sized infarcts on CT, 80% had a significant ICA or MCA lesion. In patients with a small or no infarct on CT, MCA occlusion or ICA stenosis were present in only 11%. They also suggested that the frequency of presumed thrombotic MCA occlusion was low, (probably no more than 10% to 20% of MCA occlusions), while the majority were probably embolic in origin because an arterial or cardiac source of embolus was found. Eight patients with MCA occlusion had a post mortem, and in seven the MCA was patent. They did not routinely repeat the angiogram. ICA occlusion was considered to be due to thrombosis superimposed on atheromatous stenosis (based on post mortem or endarterectomy findings in a few patients) and did not recanalise.

Fieschi et al in 1989¹²⁵ reported the results of angiography in 80 patients with acute ischemic stroke in the MCA territory studied within six hours of symptom onset. Although they included patients with large artery territory

as well as lacunar infarcts, they found that early angiography revealed cerebral arterial occlusion in 76% (66% were intracranial), and of patients who had repeat angiography (or transcranial Doppler ultrasound) within 1 week, 70% of the MCA occlusions had disappeared. Potential embolic sources, (cardiac or carotid atheroma) were found in more than 80% of patients. They also commented that patients with documented intracranial occlusion and scarce or absent collateral filling at early angiography had the worst clinical outcome.

The studies of angiography early after onset of acute ischaemic stroke are summarised in Figure 1.3.1. The earlier studies tended not to differentiate stroke by clinical syndrome (ie cortical or lacunar, carotid or vertebrobasilar territory), and were unable to differentiate cerebral infarction from haemorrhage. Some of the recent studies did not exclude (or even differentiate) lacunar infarction. Angiography was not repeated routinely in any of the studies, although the study by Fieschi et al ¹²⁵ used transcranial Doppler ultrasound to monitor arterial patency in all the patients. Of the recent studies, angiography performed within two days of onset showed occlusion in 76 to 85% of patients in the ICA or large intracranial branches. Of the patients who had repeat angiography or post mortem, 13 to 28% had persistent arterial occlusion at about one week after stroke onset and the remainder had recanalised. Some

patients died before a second angiogram could be performed and did not have a post mortem. Therefore none of these studies gives a really true idea of recanalisation rate, but taken together, they suggest that around 80% of large ischaemic strokes will have an arterial occlusion demonstrable on angiography performed within 24 hours of stroke onset, but by the end of one week only in about 25% will the artery still be occluded. Recanalisation may depend on the site and nature of the occlusion. MCA occlusions seem to recanalise frequently and quickly, whereas ICA occlusions seem to recanalise less frequently, possibly simply as a result of the larger bulk of clot in the latter. The efficacy of treatments such as streptokinase, intended to quicken thrombus lysis, must be measured against the spontaneous lysis rate, and not tested in uncontrolled trials.

Further support for the embolic nature of acute ischaemic stroke in the West comes from Gacs et al.¹²⁶ They studied the spontaneous pathway of a tiny balloon on the end of a very floppy catheter, introduced into the ICA in 42 patients being investigated for cerebrovascular disease. The most frequent sites of lodgement of the balloon were the MCA trifurcation, the angular artery branch, and the MCA main stem corresponding very closely with the distribution of spontaneous, presumed embolic, occlusions (Figure 1.3.2). From this work they were also able to conclude that many TIAs are probably due to transient embolic occlusion of

large intracranial arteries. While this may provide circumstantial support for the role of emboli, it must be remembered that the MCAs are the largest, most constant, of the basal intracranial arteries, with the most branches supplying the largest territories. Occlusion of the MCA or its branches is probably noticed more frequently by patients than PCA or ACA occlusions, therefore Gacs's work does not exclude the possibility that some intracerebral arterial occlusions are thrombotic.

The concept that embolic occlusion of the intracranial arteries is more common than thrombotic occlusion in Western peoples has probably arisen partly because of the apparently normal appearance of the underlying artery once the occlusion has lysed (plus patient selection bias), although atheroma is very common in the intracranial circulation on angiography for other reasons, such as following subarachnoid haemorrhage or in the investigation of cerebral tumours (personal observation), and even at post mortem the distinction between embolic and thrombotic occlusion may be difficult. Whatever the truth in Westerners, thrombotic MCA occlusion is considered to be more common in Oriental and Negro peoples.^{109,123} This may be because, certainly in Oriental peoples, the frequency of cervical carotid atheroma is less, therefore other risk factors come to the fore.¹⁰⁹ It may also reflect differences in the method of diagnosis, pathological techniques, etc, so these statements about the

relative importance of embolic/thrombotic occlusion must be regarded with caution.

In addition to the actual arterial occlusion, other secondary features of arterial occlusion may be seen with angiography. Taveras et al¹²¹ witnessed the effect of an accidental embolic event during angiography (needle fragment) and described vasodilatation of arteries distal to the embolus, and early venous filling in the occluded artery's territory which occurred very rapidly following cerebral arterial occlusion. The patient remained asymptomatic despite involvement of a moderate sized part of the parietal cortex, illustrating that intracranial artery occlusion may be asymptomatic. Other secondary features of cerebral artery occlusion include arteriolar-capillary block (resulting in an extremely prolonged arterial phase on angiography thought to be due to occlusion of the capillary bed) ; mass effect causing displacement of arteries ; arterial vasodilatation which may still be observed after re-opening of the occluded vessel and may be the only sign of previous vessel occlusion (thought to occur due to metabolic abnormalities) ; and finally lengthening of the circulation time in the whole of the affected hemisphere (longer than 6 seconds).¹²¹ Irino et al¹²⁷ described similar findings and in addition arterial narrowing (localised or widespread narrowing of the arterial calibre in the ACA or MCA perhaps due to spasm), capillary blush (similar to early venous filling), residual stenosis

(irregular and somewhat stenotic arterial lumen at the initially occluded point). This last could be observed during re-canalization of the artery and was not necessarily indicative of underlying atheroma.

1.3.4 Concluding comments.

Cerebral angiography has been infrequently performed in acute ischaemic stroke because of the lack of any therapy which it might influence, and its associated risks. The few studies which have been done have documented a high rate of occlusion of large intracranial arteries in patients with major ischaemic strokes studied within a few days of onset and, as suspected from post mortem studies, the occlusion may lyse spontaneously and quickly. There are no large series of patients who have had serial angiography in all cases after an MCA/ICA ischaemic stroke, but it is likely that up to 80% of MCA occlusions will have recanalised by one week after onset, and few ICA occlusions.

It is generally accepted that many large intracranial artery occlusions are embolic in Western peoples (cardio or artery-to-artery embolus), although the evidence to support this is somewhat circumstantial.

It is unlikely that angiography will be used more frequently in acute ischaemic stroke, but it is still essen-

tial for patients being considered for carotid endarterectomy. A large amount of angiography data has been generated by the European and North American symptomatic carotid endarterectomy trials which will be closely studied to try to improve understanding of the relationship between angiographic appearance of the stenosis, risk of completed stroke, and appearance at carotid endarterectomy.

Although ultrasound and magnetic resonance angiography are improving, angiography is likely to remain the "gold standard" for demonstrating cerebral arterial disease in the immediate future. Improved radiographic contrast media, properties of catheters, guidewires, and radiographic equipment mean that the risks of cerebral angiography are low but still serious. It is important to try to find other means of identifying arterial pathology which are more practical, easier, cheaper and repeatable in acute ischaemic stroke.

Summary of Chapter Three

1. Cerebral angiography with modern equipment carries a four percent risk of transient neurological deficit, and a one percent risk of permanent neurological deficit in patients being investigated for mild ischaemic cerebrovascular disease prior to carotid endarterectomy.
2. Angiography allowing visualisation of the carotid arteries spurred the development of carotid surgery to prevent major strokes.
3. Information gained from angiography in acute ischaemic stroke patients showed that intracranial arterial occlusion was frequent when performed within the first few days of stroke onset.
4. Spontaneous lysis of the arterial occlusion was observed on angiography in the 1960s and 1970s.
5. More recent angiographic studies in acute ischaemic stroke have confirmed the earlier studies.
6. It is generally considered that emboli are a frequent cause of acute ischemic stroke in Western populations (cardio- or artery-to-artery emboli).
7. Thrombosis is considered to be a common cause of ICA occlusion in the same population.
8. Spontaneous lysis of cerebral artery occlusions occurs (up to 20% at 24 hours and 80% at 1 week). This must be taken into account in the design of any therapy trials.

Recanalisation rate of occluded cerebral arteries on angiography in acute ischaemic stroke

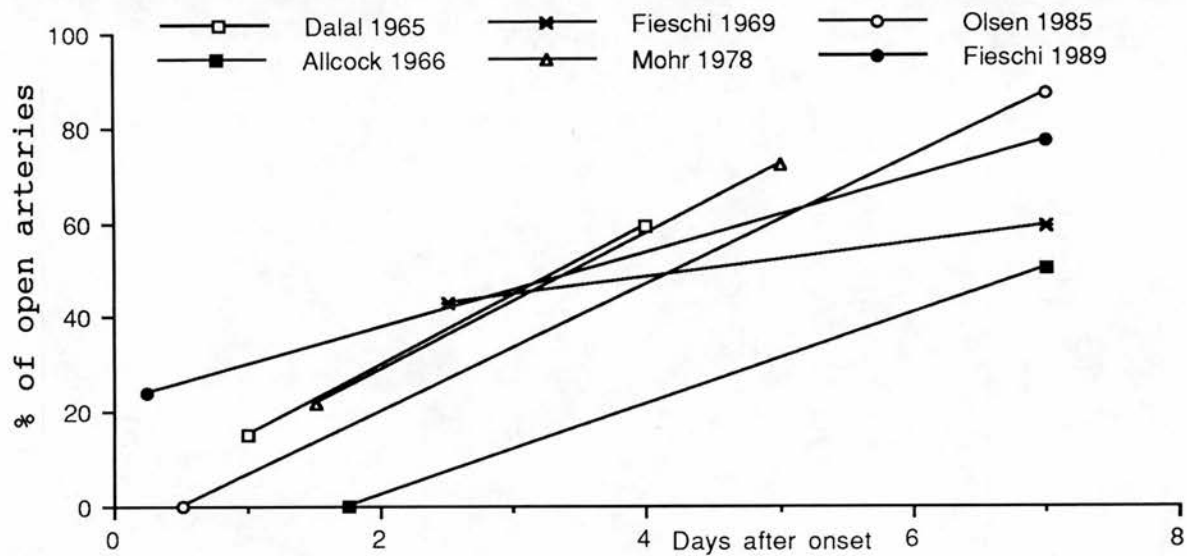


Figure 1.3.1 Estimated Recanalisation Rate of Occluded Cerebral Arteries Following Acute Ischaemic Stroke - Data pooled from all published studies which have performed initial and follow up angiography or (transcranial Doppler ultrasound) on patients within a few days of onset of acute ischaemic stroke. Dalal (119), Allcock (120), Fieschi (122), Mohr (123), Olsen(124), Fieschi (125). Note that none of the studies performed follow up angiograms on all their patients.

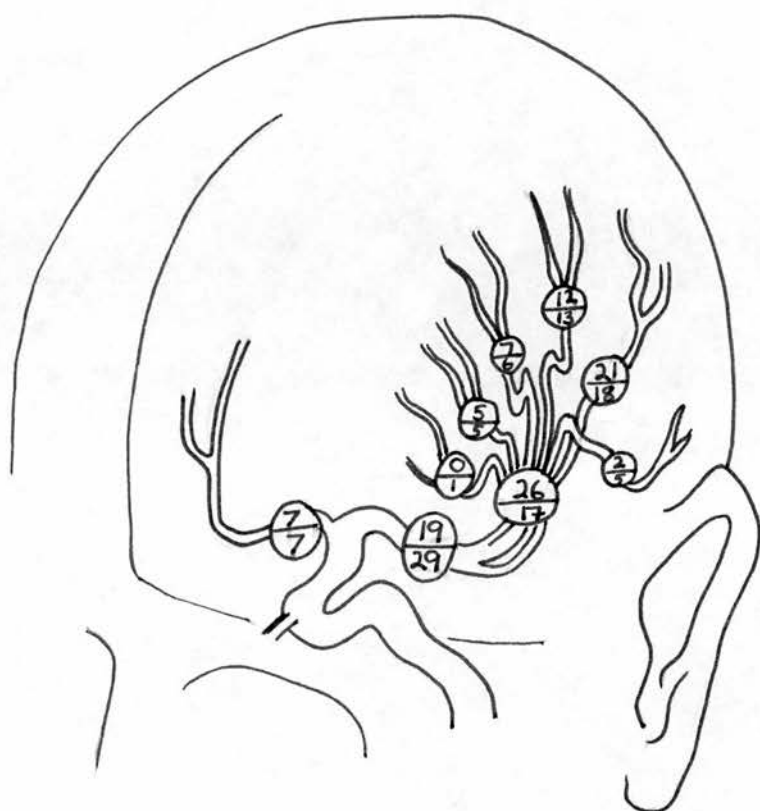


Figure 1.3.2 Distribution of Arterial Occlusions in the Middle and Anterior Cerebral Arteries Compared with the Distribution of Artificial Emboli. from Gacs et al 1982. (126) Upper numbers = percent distribution of artificial emboli (tiny balloon on a thin catheter "floated" into the internal carotid artery), lower numbers = percent distribution of spontaneous occlusions.

Part One

Chapter Four

Imaging the Cerebral Vasculature in Cerebrovascular Disease

- Non-Invasive Techniques :

Transcranial Doppler Ultrasound

1.4.1 Introduction

1.4.2 Technique and methodology of transcranial Doppler

1.4.3 Interpretation of the transcranial Doppler result

1.4.4 Studies of acute ischaemic stroke using Transcranial Doppler

1.4.5 Studies of chronic ischaemic cerebrovascular disease using Transcranial Doppler

1.4.6 The use of transcranial Doppler in other intracranial diseases

1.4.7 Concluding comments

Summary of Chapter Four

1.4.1 Introduction

Transcranial Doppler ultrasound (TCD) was developed by Rune Aaslid in the early 1980s as a non-invasive method of indirectly assessing cerebral blood flow and arterial pathology by measuring blood velocity in the basal intracranial arteries.¹²⁸ He designed a small, mobile ultrasound machine which produced a spectral waveform of the Doppler blood velocity but without simultaneous B mode imaging. In children it has been possible for several years to obtain simultaneous B mode and spectral Doppler ultrasound images of the brain through the anterior or posterior fontanelle, using standard 5 to 10 MHz general radiology Doppler ultrasound machines. This was not possible in adults because the thickness of the skull prevented transmission of the ultrasound beam. Recently low frequency, high power output ultrasound probes have been developed allowing colour flow Doppler imaging of the brain in adults using general radiology ultrasound machines.¹²⁹ Colour flow TCD is an exciting development combining a grey scale B mode image of the brain with colour flow Doppler images of the basal intracranial arteries superimposed, but is still in the early stages of development. The work for this thesis was done using a small, mobile, spectral TCD machine similar to that originally developed by Aaslid, so the following discussion will refer to spectral TCD except where indicated otherwise.

Spectral TCD equipment, because of its mobility, can be used at the patient's bedside as well as in the clinic. TCD has provided insights into acute cerebrovascular disease because it is unique among cerebrovascular imaging tools in being mobile and costing less than £30000. It is feasible to study the patient very quickly after onset of symptoms, and lack of patient cooperation is not generally a problem unless it is extreme. This contrasts with all the other cerebrovascular imaging tools, (including CT scanning) which require the patient to keep still for at least ten seconds at a time (usually much longer - 20 minutes), are immobile, and, with the possible exception of a simple gamma camera, cost in excess of £500000. In this chapter the technique of TCD, problems with interpretation of results, its sensitivity and specificity in acute ischaemic stroke, and the useful information which it has provided thus far will be discussed.

1.4.2 Technique and methodology of TCD

TCD uses the Doppler principle to measure blood velocity in the basal intracranial arteries - MCA, ACA, PCA, basilar artery and intracranial ICA. Ultrasound measurement of blood velocity by the Doppler principle uses the difference between the frequency of the emitted sound beam and the returning sound beam reflected off the moving red blood cells to calculate the blood velocity taking account of the

angle of incidence of the beam to the moving column of blood. Moment to moment velocity is calculated by a fast Fourier transform technique to yield a constant signal output which gives "instantaneous" measures of blood velocity.¹³⁰ Using a "pulsed" ultrasound output, the depth of recording can be adjusted to sample individual points along the length of a vessel. Standard spectral TCD equipment, as developed by Aaslid, allows sampling at five mm intervals.¹³¹

Doppler shift frequency $dF = 2 F_e \cdot v \cdot \cos A / c$

where F_e = emitted ultrasound frequency

v = calculated velocity from Doppler shift

A = angle of insonation of ultrasound beam to artery or vein

c = velocity of sound in the body

(= 1540 ms^{-1} for practical purposes)

The Doppler shift can be expressed in KHz, or in cms^{-1} if the angle of insonation is known. As the Doppler frequency shift depends on the angle of the ultrasound beam to the moving blood, absolute velocity may not be the same as perceived velocity if the angle of incidence is not known. If the angle of insonation is 0 - 30 degrees, its cosine will be 1 to 0.86, incurring a maximum difference of less than 15% between absolute and perceived velocities. However if the angle is greater than 30 degrees, considerable errors may result from velocity readings which are much lower (or

much higher) than reality. In extracranial duplex Doppler ultrasound, where the vessel is imaged (B mode) simultaneously with the spectral Doppler waveform, the angle of insonation can be measured exactly, but in spectral TCD there is only the Doppler signal, so it is assumed that the artery is running parallel to the ultrasound beam so that the angle of incidence of the beam to the vessel is no more than 30 degrees.¹²⁸ This may not be valid, as the basal intracranial arteries may be tortuous. Limited experience with colour flow TCD has already suggested that the angle of incidence of the ultrasound beam to the MCA is often greater than 0 - 30 degrees therefore the absolute blood velocity in the MCA is likely to be higher than the perceived velocity.¹³² On the other hand, the normal range of blood velocities found with spectral TCD has been established from study of large numbers of "normal" subjects, and is likely to include a wide range of different degrees of arterial tortuosity.^{128,133,134,135,136}

TCD uses a 2 MHz ultrasound probe and a much higher power output than is used for ultrasound of soft tissues. These modifications are necessary for transmission of the ultrasound beam through the skull bones. There are only certain parts of the skull which are sufficiently trans-sonic for ultrasound access. These "windows" to the cerebral vessels are the temporal bone, where there is usually a sufficiently thin area just above the zygomatic arch, the

orbit, and the foramen magnum (Figure 1.4.1). The power output must be reduced to 10% of that used for trans-temporal imaging when using the orbital window, to prevent damage to the eye. Standard adult TCD equipment should not be used in children; their thinner skulls allow greater ultrasound penetration and there is a theoretical risk of damage to the brain from the high power output.

The MCAs, ACAs, and PCAs may be insonated through the temporal window. The M1 and M2 segments of the MCA are assumed to run directly towards the probe, and the A1 segment of the ACA directly away, hopefully optimising the angle of insonation for velocity measurements. However the intracranial arteries are frequently tortuous, particularly in the elderly, which may invalidate these assumptions.^{129,137} Colour-flow TCD has shown even in limited series that angles of insonation to the MCA of up to 50 degrees are common.¹²⁹ Generally it is necessary to move the probe over the temporal region and adjust the probe angle until the "best" signal at the required depth is obtained, "best" being highest velocity and most intense signal, and this is assumed to be the closest to an angle of incidence of zero. The ICA siphon, ACA, and ophthalmic arteries are insonated through the orbit, the basilar artery through the foramen magnum, and the vertebral arteries through the foramen magnum or in the upper neck behind the mastoid process.

TCD is very operator dependant, and although an

experienced operator may take only ten minutes to complete a study in a cooperative patient, in a restless and confused patient it can take longer than half an hour to obtain satisfactory signals from all the basal intracranial arteries.

1.4.3 Interpretation of the TCD result.

Normal values for blood velocity in the MCAs, ACAs, PCAs and ICAs have been established: peak systolic and mean velocity, and the pulsatility index. The mean velocity may be expressed in different ways, for example the "time-mean" velocity is calculated from the outline of the spectral display and is the mean velocity during one cardiac cycle, not taking account of the density of Doppler frequencies.¹²⁸ The "spatial-mean" velocity is more complex and is the average Doppler velocity weighted by the spectral density; that is, the relative intensity of the Doppler signal at each velocity.¹³⁰ In TCD it is impossible to know what the sample volume encloses as the artery cannot be imaged, and the signal to noise ratio is poor, so the most practical Doppler reading of velocity is that of the spectral envelope or outline, ie time-mean velocity. The "time-mean" velocity will be used in this thesis unless otherwise stated, as that is what is calculated automatically by the EME TCD machine. The pulsatility index (PI) may also be calculated in differ-

ent ways and is a measure of cerebral arterial resistance. In this thesis the PI used will be the peak systolic minus end diastolic velocity/time mean velocity, as that is what is calculated by the EME TCD machine. These are summarised in Table 1.4.1.^{128,133,134,135,136}

Cerebral arterial blood velocity declines with age (Table 1.4.1). Note also that the velocities in the two MCAs should not differ by more than 21%, the ACAs by 27%, and the PCAs by 28% in normal subjects.¹³⁸ Serial TCD studies in normal subjects have shown that the MCA, ACA, and PCA blood velocities vary by less than 20% during the day, and between days.¹³⁹

In up to ten percent of subjects it is impossible to obtain a satisfactory signal through the temporal bone window because the bone is too thick (particularly in elderly females), or because the artery takes a very tortuous course.^{140,141} In ten to twenty percent of normal individuals one or other of the ACAs cannot be identified, and one or other of the PCAs in twenty to thirty percent. This is because of anatomic variants of the circle of Willis, vessel tortuosity, and poor bone windows.^{128,133,142,143}

Several other factors influence cerebral blood velocity and must be taken into account when interpreting TCD. The patient's PaCO_2 ¹⁴⁴ is probably the most important variable, as even minor changes may produce marked increase or decrease in cerebral arterial blood velocity. Other factors

which may affect velocity readings include haematocrit,¹⁴⁵ patient posture,¹⁴⁶ mental activity (eg eye opening when recording from the PCA),^{147,148,149} intracranial pressure,¹⁵⁰ and respiratory pattern (eg Cheyne-Stokes respiration because of alterations in PaCO_2).

A final major problem with interpretation of the TCD signal is illustrated in Figure 1.4.2 and is a problem for Doppler studies of blood vessels anywhere in the body. The Doppler signal is not just a reflection of vascular status at the sampling point in the vessel (vessel diameter and flow rate), but reflects factors up and down stream from the sampling point. For example, vasodilatation of the pial arteries as occurs with hypercapnia causes increased blood velocity in the MCA M1 segment without any change in the calibre of the M1 segment itself. An ICA occlusion in the neck might result in reduced blood velocity recorded from the ipsilateral M1 segment without any abnormality of the M1 segment itself. In Figure 1.4.2, three possible Doppler signals which might be obtained proximal to an occlusion at the origin of the first main branch of the MCA are illustrated. The recording from the asymptomatic MCA is shown for comparison. The Doppler velocity in the symptomatic MCA might be reduced, or the same as, or increased compared with the asymptomatic MCA blood velocity, depending on the relative contribution of increased flow through the patent branch to collaterals. If the flow in the patent branch was the

same as it had been before the embolic occlusion, then only half of the original pre-occlusion amount of blood would be flowing through the M1 after the occlusion, so the Doppler signal would be reduced. If the patent branch supplied some collaterals (resulting in increased flow in the patent branch compared with the pre-occlusion state) then the increase in flow might be sufficient to keep the flow in the M1 the same as it was prior to the occlusion. This would mislead the investigator to think that the symptomatic MCA was "normal". If the patent branch supplied lots of collaterals, then it might be possible to have increased flow in the M1 after the occlusion compared with the pre-occlusion flow, causing a higher blood velocity than on the asymptomatic side. There is no way of knowing, on an isolated measurement, which of these is occurring. Serial measurements to chart the change in blood velocity with time is one possible way of sorting this out, but retrospectively. A similar problem arises when trying to decide whether increased velocity in the symptomatic artery is due to spasm or hyperaemia in patients with a head injury or subarachnoid haemorrhage. In these situations, reduced PI tends to indicate hyperaemia, and increased (or less reduced) PI spasm, but the relationship between the two is still being evaluated.^{151,152}

1.4.4 Studies of acute ischaemic stroke using transcranial Doppler ultrasound

Several studies have been published concerning the use of TCD in acute ischaemic stroke. Mattle et al in 1988¹⁵³ compared TCD findings with conventional intra-arterial angiography in 61 patients with MCA territory TIAs, minor and major ischaemic strokes and 535 healthy subjects. Patients had MCA main stem occlusion, branch occlusion, or MCA stenosis as judged by CT, angiographic and autopsy findings. The TCD and angiogram examinations were performed over a wide range of time intervals up to one year (TCD a mean of 32 days and angiography a mean of 53 days) after symptom onset. They found that patients with MCA main stem occlusion had a substantial reduction in MCA blood velocity compared with the asymptomatic MCA, and increased velocity in the ipsilateral ACA (to supply collaterals to the MCA territory). The reduction in symptomatic MCA blood velocity was much greater if there was ipsilateral ICA disease also. MCA branch occlusion caused a minor reduction in blood velocity. In all three situations the symptomatic MCA blood velocity values showed a wide standard deviation.

Zanette et al¹³⁸ compared intra-arterial digital subtraction angiography and TCD in 39 patients within four hours of onset of acute ischaemic stroke in the MCA territory. The symptomatic MCA blood velocity was least in MCA origin or main stem occlusion, with or without ICA occlu-

sion. The symptomatic MCA blood velocity was less reduced or normal if only an MCA branch was occluded. They found increased velocity in the ipsilateral ACA in one third of patients, implying collateral supply to the ischaemic MCA territory. Zanette et al devised the "asymmetry index" for blood velocity in the symptomatic and asymptomatic MCAs based on these findings. Asymmetry of the MCA blood velocities of greater than 21%, of the ACA of greater than 27%, and the PCAs of greater than 28% was indicative of proximal artery occlusion.

Kaps et al¹⁵⁴ evaluated TCD against angiography in 23 patients within 24 hours of acute MCA occlusion. TCD was most suggestive of MCA occlusion when all ipsilateral basal arteries except the MCA were detected. Increased blood velocity in the ipsilateral ACA was useful corroborative evidence of MCA occlusion (proportion of patients not stated). Frequent follow up TCD examinations revealed evidence of reperfusion (symptomatic MCA blood velocity becoming detectable or increasing from the admission value) in 60% of patients. The blood velocity was frequently normal in the MCA main stem in MCA peripheral branch occlusions. In some patients an increase in the symptomatic MCA blood velocity (higher than that in the asymptomatic MCA) occurred a few days after symptom onset, which when focal, was thought to be due to a stenosis appearing during recanalisation, and when diffuse, to hyperaemia.

Three further studies confirm these findings. Ley-Pozo and Ringelstein¹⁵⁵ compared TCD with intra-arterial DSA in 133 consecutive hospital-admitted patients with MCA territory ischaemic symptoms including TIAs. The time of each study after symptom onset was not stated. They found good agreement between TCD and angiographic evidence of stenosis and/or occlusion in the carotid siphon and MCA. TCD had a sensitivity of 92 (95% confidence interval (CI) 73-99) and specificity of 97 (95% CI 92-99) for detecting obstructive lesions compared with angiography.

Kushner et al¹⁵⁶ compared TCD with angiography in 42 acute ischaemic stroke patients within six hours of symptom onset. Reduced MCA velocity was found in 21/21 patients with proximal MCA occlusions but only 1/8 patients with peripheral MCA branch occlusions. TCD showed normal MCA blood velocity in 2/5, and absent MCA blood velocity in 3/5 patients with ipsilateral ICA siphon stenosis but a patent MCA on angiography. TCD was normal in all eight patients with normal angiograms. 18/29 patients showed evidence of recanalisation with increase in the symptomatic MCA blood velocity on sequential examinations up to one week after symptom onset.

Handa et al¹⁵⁷ compared TCD with angiography in 42 patients with cerebrovascular disease. TCD showed normal MCA blood velocities in patients with normal angiograms, but reduced blood velocity in patients with ipsilateral ICA

siphon or MCA stenosis or occlusion, giving an accuracy of 87% for TCD for detecting occlusive lesions (including stenoses) of the intracranial ICA and MCA.

Thus, reduced blood velocity in the symptomatic MCA on TCD correlates well with MCA main stem or major branch occlusion, or ICA siphon occlusion/stenosis, but may be normal in small MCA branch occlusions. Recanalisation is associated with an increase in blood velocity in the symptomatic MCA to a value nearer to that on the asymptomatic side. The symptomatic MCA blood velocity may rise above that on the asymptomatic side if a stenosis develops at the point of previous occlusion during recanalisation, resulting in a focal, high, turbulent velocity in the MCA main stem. Hyperaemia may also result in increased velocity in the MCA main stem, usually more diffusely along the entire length of the MCA recordable by TCD than in a focal stenosis, though it may be difficult in some patients to distinguish between stenosis and hyperaemia with TCD.¹⁵⁴ The effect of morphologic changes in ischaemic tissue in the MCA territory, such as oedema leading to hemispheric swelling, on the MCA blood velocity and pulsatility have not been studied closely enough to be certain what effect they would have. Focal haematomas may displace the MCA from its normal insonation position, and by stretching it may cause a focal velocity increase (personal observation).

1.4.5 Studies of chronic ischaemic cerebrovascular disease using Transcranial Doppler.

In the diagnosis of chronic intracranial arterial disease, Spencer and Whisler studied 300 patients presenting with TIA, minor stroke or dizziness and found a sensitivity of 73% and specificity of 95% for detection of significant stenosis or occlusion of the ICA siphon and MCA main stem (compared with conventional angiography).¹⁵⁸

Lindegaard et al¹⁵⁹ compared TCD with angiography in eleven patients with intracranial ICA and MCA stenoses and found a clear inverse relationship between residual lumen diameter on angiography and Doppler flow velocity. Focal stenosis caused a localised high velocity jet with turbulence, and distally a reduced and damped velocity waveform.

Grolimund et al compared TCD with angiography in 95 patients with TIA and minor stroke and found TCD had a sensitivity of 91% and a positive predictive value of 94% for detecting intracranial ICA and MCA stenoses and occlusions.¹⁴¹ They also found that TCD was able to detect with an accuracy of 94%, collateral flow over the Circle of Willis in the anterior communicating artery, and of 88% in the posterior communicating arteries.

Hennerici et al found good correlation between TCD and angiography for detecting stenoses of 80% or more in the basal intracranial arteries in 39 patients with TIA or minor

stroke.¹⁶⁰ They were also able to identify collateral arterial pathways such as reversed flow in the ACA ipsilateral to an ICA occlusion, reversed flow in the MCA peripheral to an MCA main stem occlusion, and flow from the basilar artery to the distal ICA through the posterior communicating artery in proximal ICA occlusion.

Evaluation of the vertebrobasilar arteries with TCD is less reliable for detecting stenoses and occlusions. Firstly it is more difficult to detect the PCAs,^{128,133,134,135} and there is more variation of normal in the posterior circulation anatomy.^{72,75} Mull et al found TCD was unreliable for diagnosing significant vertebral or basilar artery stenosis or occlusion (compared with angiography) in 37 patients with vertebrobasilar TIAs and ischaemic strokes. They were unable even to identify the proximal basilar artery in 30% of patients.¹⁶¹

1.4.6 Use of Transcranial Doppler Ultrasound in other intracranial diseases

TCD has been used to assess the intracranial arteries in diseases other than ischaemic stroke, such as:

- a) the diagnosis of vasospasm following subarachnoid haemorrhage,¹⁶²
- b) identification of the feeding arteries of arteriovenous malformations and monitoring the haemodynamic effects of their treatment,¹⁶³
- c) confirmation of the clinical diagnosis of brain death¹⁵⁰
- d) intensive care unit monitoring of brain-injured patients,¹⁴⁰
- d) intraoperative and post operative monitoring of neurosurgical patients,¹⁴⁰
- e) intraoperative monitoring of patients undergoing carotid endarterectomy to detect cerebral emboli,¹⁶⁴
- f) investigation for patent foramen ovale in young patients with acute ischaemic stroke of probable embolic origin,¹⁶⁵ and,
- g) detection of emboli of cardiac and possibly atheromatous origin in the cerebral arteries.¹⁶⁶

Despite this, TCD remains largely a research tool, albeit an extremely useful one.¹⁶⁷ This is particularly true in acute ischaemic stroke, because as yet, there is no effective treatment which might be guided by knowledge of cerebral arterial pathology.

1.4.6 Concluding comments

TCD is a useful research tool in acute ischaemic stroke to study patterns of arterial occlusion. Reduced velocity in the symptomatic MCA main stem with respect to the asymptomatic MCA is good evidence of MCA main stem or major branch occlusion, but normal blood velocity does not completely exclude an important MCA occlusion. Increased blood velocity in the ipsilateral ACA and PCA (to supply collateral arteries to the ischaemic MCA territory) is useful confirmatory evidence of MCA main stem or large branch occlusion. Gradual increase in the blood velocity in the symptomatic MCA during the days after an acute ischaemic stroke is good evidence of MCA recanalisation. Significant intracranial ICA or MCA stenoses may be identified, but vertebrobasilar stenoses and occlusions less reliably. TCD has technical limitations, some of which, for example inability to correct for the true angle of incidence of the ultrasound beam to the artery, may be overcome by colour flow Duplex TCD which however is less mobile. The lack of a proven treatment for acute ischaemic stroke means that knowledge of cerebral arterial occlusion in the acute phase is academic. But if a treatment was shown to be beneficial, especially in a subgroup of acute ischaemic stroke, then TCD would be one quick safe way of identifying those patients for treatment.

Summary of Chapter Four

1. TCD is a safe, non-invasive method of measuring cerebral blood velocity in the basal intracranial arteries.
2. TCD is a well established research technique in ischaemic cerebrovascular disease.
3. TCD requires an experienced operator for best results.
4. TCD is unsuccessful in up to 10% of subjects for technical reasons.
5. Cerebral blood velocity declines with age, so the relative difference between blood velocities in symptomatic and asymptomatic arteries is a more useful indicator of disease than the absolute value.
6. The difference in mean velocity between the two MCAs should be no greater than 21%.
7. Absence of the ACA or PCA signal may not be a reliable indication of disease in those vessels because of the frequent anatomic variations of the circle of Willis.
8. Reduced MCA blood velocity correlates well with occlusion of the M1 or M2 segments, but not with peripheral branch occlusions.
9. Increased velocity in the ipsilateral ACA is good corroborative evidence of MCA stenosis or occlusion.
10. In the MCA a focal stenosis causes a focal increase in blood velocity, whereas hyperaemia causes an increase in blood velocity throughout the measurable length of the

artery.

11. Should a treatment for acute ischaemic stroke become available, TCD would be one method for diagnosing cerebral arterial occlusion before treatment, and of monitoring the response to treatment.

Table 1.4.1 Normal reference values for blood velocity in the basal intracranial arteries as measured using TCD. 127,132,133,134,135

	AGE	MEAN	RANGE (+/-2SD)
MCA			
peak velocity	<40	94.5	67.3 - 121.7
peak velocity	40-60	91.0	57.2 - 124.8
peak velocity	>60	78.1	58.1 - 108.1
mean velocity	<40	58.4	41.6 - 75.2
mean velocity	40-60	57.7	34.7 - 80.7
mean velocity	>60	44.7	22.6 - 66.9
pulsatility index	20 - 45	0.71	0.51 - 0.91
pulsatility index	46 - 63	0.94	0.66 - 1.22
ACA			
peak velocity	<40	76.4	42.6 - 110.2
peak velocity	40-60	86.4	46.2 - 126.6
peak velocity	>60	73.3	32.7 - 113.9
mean velocity	<40	47.3	21.3 - 73.3
mean velocity	40-60	53.1	32.1 - 74.1
mean velocity	>60	45.3	18.3 - 72.3
PCA			
peak velocity	<40	53.2	30.6 - 75.8
peak velocity	40-60	60.1	19.1 - 101.0
peak velocity	>60	51.0	27.2 - 74.8
mean velocity	<40	34.2	18.6 - 50.0
mean velocity	40-60	36.6	17.0 - 56.4
mean velocity	>60	29.9	11.3 - 48.5

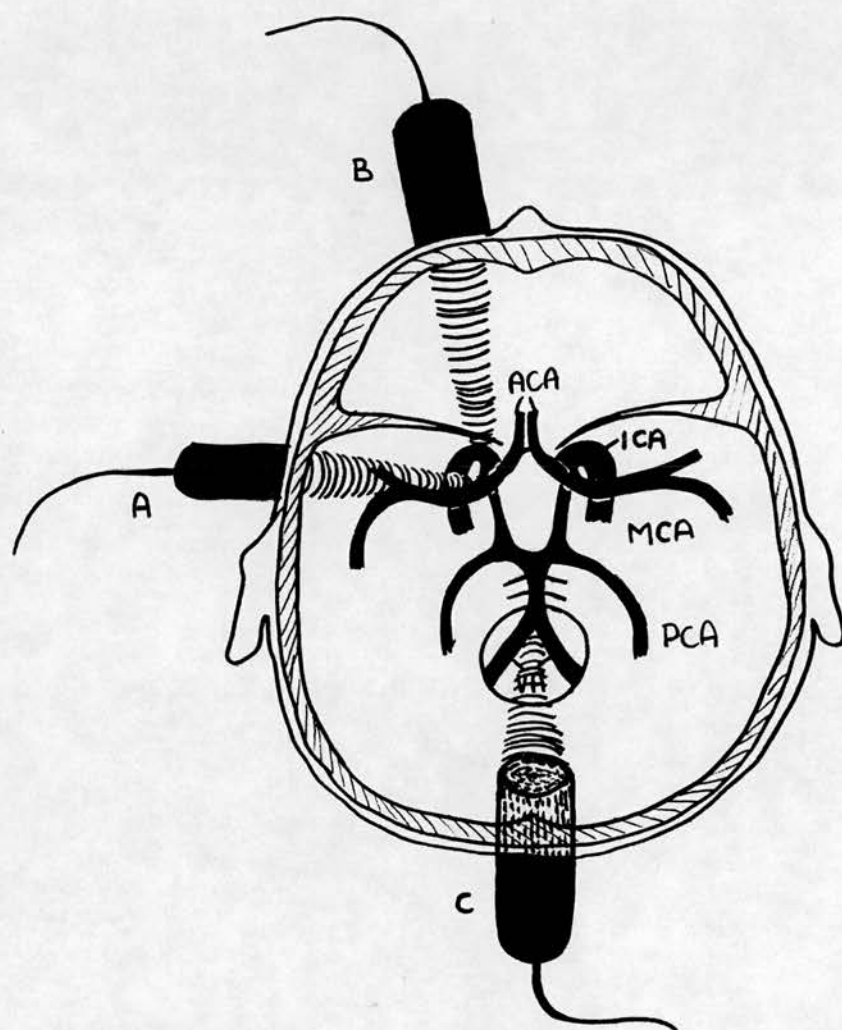


Figure 1.4.1 Windows for Obtaining Doppler Signals from the Basal Intracranial Arteries on Transcranial Doppler Ultrasound Examination. A) Temporal bone window immediately anterior to the tragus and superior to the zygomatic arch, B) transorbital, through the globe (power output must be reduced to 10% of that used for through bone transmission), C) foramen magnum.

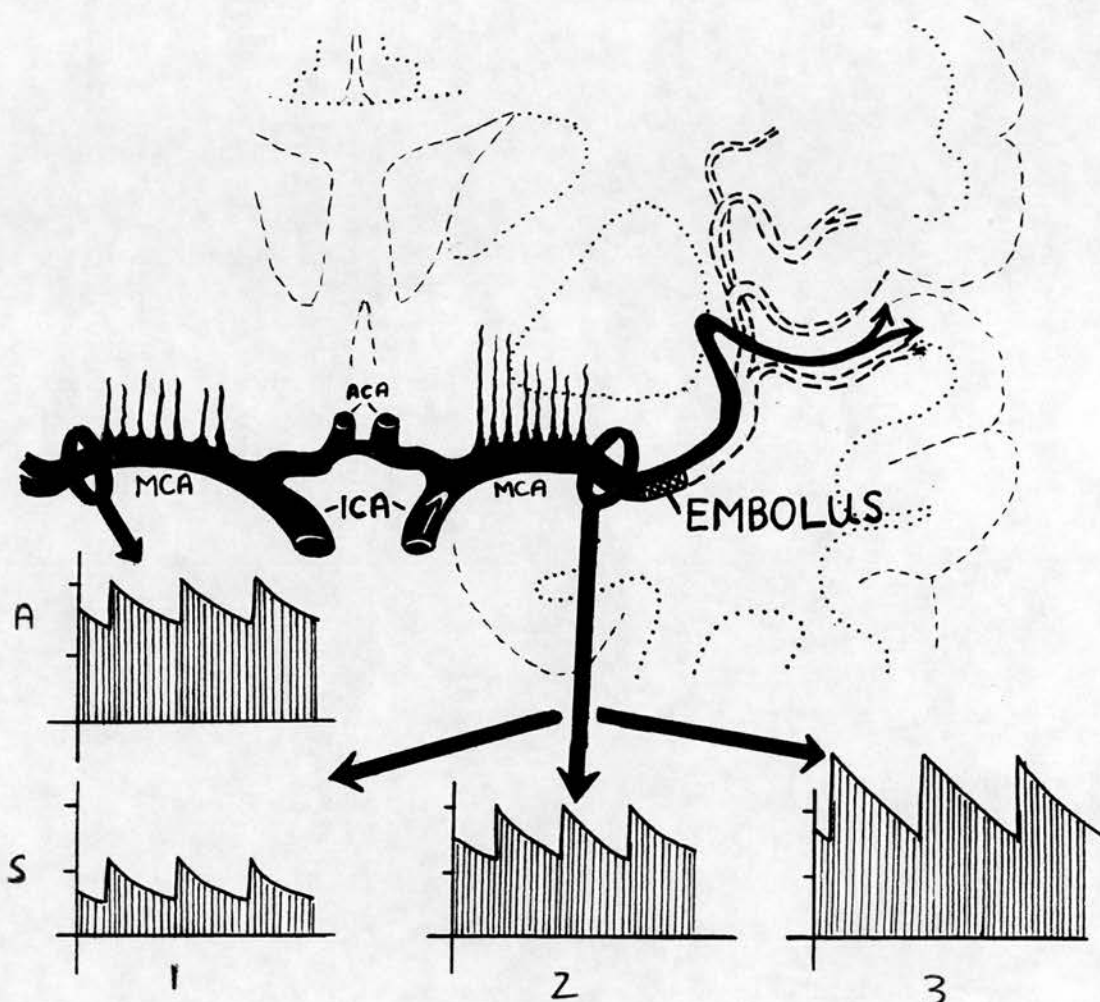


Figure 1.4.2 Possible effect of an occlusion at the first main branch of the MCA on the Doppler blood velocity recorded from the MCA main stem.

A = Doppler signal from the asymptomatic MCA.

S = Doppler signal from the symptomatic MCA : 1 = reduced velocity, 2 = velocity apparently "normal" (ie equal to the asymptomatic MCA blood velocity) because of increased flow in the still patent MCA branch, 3 = velocity increased because of hyperaemic flow in the patent branch, but could also be observed following lysis of the embolus with hyperaemic flow in the previously occluded branch. Further discussion is given in the text.

Part One

Chapter Five

Imaging of the Cerebral Vasculature in Cerebrovascular Disease - Non-invasive Techniques for Measuring Cerebral Blood Flow

1.5.1 The history of methods of measuring cerebral blood flow, including Kety and Schmidt's modification of the Fick principal

Clinical methods of measuring cerebral blood flow:

1.5.2 Positron Emission Tomography

1.5.3 Single Photon Emission Tomography

1.5.4 Xenon Computed Tomography

1.5.5 The first pass technique of assessing the cerebral circulation

1.5.6 Development of the Mean Cerebral Transit Time technique

1.5.7 Validation of the Mean Cerebral Transit Time technique, and preliminary clinical results

1.5.8 Potential advantages of the Mean Cerebral Transit Time technique

Summary of Chapter Five

1.5.1 The history of methods of measuring cerebral blood flow

Attempts to measure cerebral blood flow (CBF) began in the nineteenth century. Prior to that, observations in experimental animals led to the idea that the intracranial cavity had a fixed volume, and that variation in the volume of one of the compartments (brain, blood or cerebrospinal fluid) could only occur if there were compensatory changes in the other compartments.¹⁶⁸

Control of CBF was thought to be passive, and follow haemodynamic changes outside the brain. Roy and Sherrington in 1890 were the first to suggest that local changes in CBF might result from local variation in functional activity of the brain, so that the brain might have more control than other organs over its blood flow,¹⁶⁹ but this idea was strongly criticised.

The first practical attempts to measure CBF in patients were based on the Fick principal. In 1870, Adolf Fick had described a method of measuring cardiac output or blood flow based on the idea that cardiac output could be calculated from the total quantity of a tracer, in this case oxygen, taken up by (or removed from) the blood, divided by the net mean concentration difference between the arterial and venous blood, provided that the system was in equilibrium and the blood flow was constant during the period of measurement.¹⁶⁸ Adaptations of the Fick principal have since

been used to measure blood flow to any part of the body including the brain.

In 1945 Kety and Schmidt applied the Fick principal to the measurement of CBF in man using nitrous oxide: The amount of inert gas taken up by the tissue per unit of time is equal to the quantity brought to the tissue by the arterial blood minus the quantity carried away in the venous blood.^{170,171}

They converted the Fick principal to differential form and made it applicable to the accumulation of an exogenous non-metabolised substance in the brain, rather than the absorption of oxygen by the lungs. It was necessary to measure concentrations of tracer in arterial and mixed venous blood and the amount of tracer taken up by the brain as a whole.

$$dQ/dt = F(C_a - C_v)$$

where Q = quantity of inert gas in the brain

F = total cerebral blood flow

C_a and C_v = concentration of tracer in arterial and internal jugular blood.

t = time

Because there was no way of measuring continuously the amount of tracer taken up by the brain, it was necessary in the original method to permit virtual equilibrium to be established over a period of at least ten minutes when the amount of tracer in the venous blood became close to that in the brain. The original method used N_2O continuously inhaled

at low concentration. Kety verified experimentally that for normal brain and most abnormal situations (except major cerebral infarction) ten minutes equilibration was sufficient, with an error of only 5%. As CBF and cerebral metabolism are closely linked, it was then possible to quantify the rate of cerebral oxygen or glucose consumption with the help of Fick's principle, by measuring the cerebral arteriovenous difference and multiplying this by the CBF. Other tracer techniques developed from this but some involved direct carotid injection and jugular venous sampling so had the disadvantage of being invasive and only measuring CBF in one hemisphere at a time. In the late 1940s, the direct and indirect (inhalation of tracer) methods were compared and found to give the same results, and so gained in acceptance.¹⁶⁸ An important point to note about Kety's method is that during the equilibration process, the rate limiting factor was not diffusion between capillaries and surrounding tissue, but the disparities between tissues with different perfusion rates and partition coefficients and the rate at which tracer concentration in the tissue with the slowest perfusion approached that in the rest of the brain.

Kety's technique has been applied in a wide variety of clinical settings, and opened the door to modern study of CBF. His original technique measured total CBF, but his equations have been adapted and form the basis for regional cerebral blood flow measurement (rCBF) using inert diffusa-

ble tracers, and also clearance, autoradiographic and emission tomographic techniques.^{172,173,174} The following phases of the uptake cycle have been used to calculate blood flow :

1. the rate of tracer wash in (eg xenon CT)
2. the rate of tracer wash out (eg beta particle emitters ^{85}Kr)
3. total quantity of tracer delivered (autoradiography, microspheres and some compounds used for imaging with single photon emission tomography)
4. the variation of amount of tracer present with time (first pass techniques)

There are important differences in what is being measured between the first three and the fourth which will be discussed below, the main one being that first pass techniques measure transit time not flow.

Tracers may be divided into two broad categories: a) non-diffusible, which remain intravascular and are assayed during their first passage through the brain, are useful for first pass techniques and measurement of absolute flow (ml min^{-1}); and b) diffusible tracers which equilibrate with extravascular tissues and may be used to measure wash-in, wash-out, or perfusion ($\text{ml}/100\text{gbrain}/\text{min}$). Most modern tracers have been designed to avoid the need for arterial sampling. An ideal tracer should not be metabolised, should not alter any physiological variable (including blood flow) and should be readily and accurately detectable. Nitrous

oxide, as used in Kety and Schmidt's original work, is unsuitable because at the concentration used it has analgesic properties. Recirculation of tracer may affect washout measurement and must be corrected for. Suitable diffusible tracers include isotopes of xenon, krypton, iodine, halogenated compounds, oxygen and more complex molecules such as N-isopropyl- ^{123}I -paraiodo-amphetamine (IMP) and $^{99\text{m}}\text{Tc}(\text{d,l})$ hexamethyl propylene amine oxime (HMPAO). Some may be inhaled and others injected intravenously making the techniques more practical. The behaviour of some of these molecules is not entirely clear and their use in clinical practice is based on several assumptions which may not be valid. Furthermore, their behaviour in damaged brain has not been well quantified. For example, HMPAO used in SPECT imaging consists of a mixture of lipophylic and hydrophylic forms and in vivo and in vitro the lipophylic form is rapidly converted to the hydrophylic.¹⁷⁵ Only the lipophylic form is taken up by the brain with an efficiency of close to 100%, but the actual uptake depends on the fraction to reach the brain in the lipophylic form.¹⁷⁶ The relationship between HMPAO uptake and regional cerebral perfusion is not linear.¹⁷⁷ Recirculation occurs to a certain extent. The cerebral distribution of HMPAO is principally a reflection of regional cerebral blood flow, though may be influenced by lipid mass and red blood cell volume.¹⁷⁵ Cerebral retention of HMPAO may be secondary to conversion of the lipophylic to

hydrophylic forms which cannot diffuse out through the cell membrane, so it is possible that HMPAO may not distinguish viable from dead but perfused tissues.¹⁷⁸ There is no way of measuring absolute uptake, only relative uptake, therefore absolute perfusion cannot be calculated. However the advantages are that the distribution changes little with time allowing imaging up to two hours after injection.

The "commonly" available methods of assessing cerebral blood flow using tracers will be discussed in turn. It should be noted that none are really "commonly" available, for example to a district general hospital, though a few are inexpensive and practical enough to become more widely available in future.

1.5.2 Positron Emission Tomography

Positron emission tomography (PET) was introduced in the early 1960s. It uses very expensive equipment, very expensive short-lived radioisotopes (generated by a cyclotron near the PET scanner), and is very expensive to maintain¹⁷⁴. Consequently there are only about fifty operating in the whole world. Positrons, emitted as part of the radioactive decay of some radioisotopes, react with electrons nearby and this annihilation reaction releases two gamma photons with equal energy which travel in opposite directions. Only the photons reaching the detectors in the PET scanner simultaneously are recorded thus giving very accu-

rate tomographic information on regional cerebral metabolism and blood flow. Radioisotopes of elements that are normal constituents of biological molecules (^{11}C , ^{13}N , ^{15}O), or ^{18}F , ^{68}Ga , ^{75}Br linked to biologically active molecules may be used as tracers. Methods of measuring rCBF with PET use ^{15}O -labelled water as the radiotracer (washout) which is biologically inert, chemically stable and has a short half life permitting repeated measurements with little time delay. CO_2^{15} is inhaled and rapidly converted to H_2O^{15} by carbonic anhydrase in the red blood cells and circulates to the brain until after ten minutes a steady state is reached and rCBF can be measured from the rate of washout.¹⁷⁴

The limitations of PET arise from the non-linear relationship between rCBF and measured tissue radiotracer concentration. At higher flow levels, a large change in rCBF produces a relatively smaller change in brain ^{15}O concentration, and as a result, a given error in measurement of tissue radioactivity produces increasingly larger errors in the measurement of flow as flow increases. Errors occur due to statistical variations in radioactive decay, scattered radiation, in measuring the concentration of tracer in the arterial input, and in assumptions about the blood-brain barrier partition coefficient. The partition coefficient may change in a variety of disease states, notably ischaemia. In areas with heterogeneous flow patterns (such as occurs in an infarct) rCBF measured in this way is inaccurate as the

method assumes that the region of interest is of uniform composition and physiologic properties.¹⁷⁹ A second PET method of measuring rCBF, less prone to errors, uses a freely diffusable tracer (H_2O^{15}) administered intravenously as a bolus and the distribution in the brain then measured, and compared with the tracer concentration in arterial blood measured simultaneously with the scan, assuming that the amount of tracer in each part of the brain is proportional to the blood flow into it and nothing else.¹⁷⁵ Obviously in some disease states with blood-brain barrier breakdown this assumption is not valid, but overall this second technique is thought to be more accurate.¹⁸⁰

In acute ischaemic stroke it is possible to measure regional cerebral blood flow (rCBF) and volume (rCBV), regional cerebral metabolic rate for oxygen (rCMRO_2) and glucose (rCMRG) and relate the alteration in rCBF to the metabolic consequences in fairly small areas of brain. However, acute stroke is logistically difficult to study with PET.¹⁸¹ Difficulties arise in getting the patient to the scanner quickly, ensuring that the isotope is available when needed, patient cooperation, and caring for the patient while in the scanner. Despite this, the few studies which have been done have yielded important insights into the pathophysiology of brain ischaemia. The principal findings are that within the first 24-36 hours, cerebral tissue in and around the area of depressed flow exhibits a raised

oxygen extraction fraction (OEF)¹⁸² indicating that in the acute phase some ischaemic cerebral tissue is surviving by using the normal reserve in oxygen carriage. This strongly suggests that during the first day or so after stroke onset some areas of cerebral tissue are surviving and that improved flow would allow an increase in the rate of oxygen utilisation by the tissue. About one week after the stroke, the OEF falls to less than normal, and the rCBF improves (either due to spontaneous recanalisation, collateral flow or neocapillary growth). Sometimes greatly increased flow has been found in keeping with the concept of luxury perfusion. Increased glucose and decreased oxygen utilisation has been observed, thought to be due to infiltration of white blood cells, as has been shown on histological studies.¹⁸² In chronic infarction (one month or more after onset), blood flow and oxidative metabolism are reduced in and around the lesion, and glucose/oxygen utilisation reverts to its normal ratio indicating that the tissue is permanently damaged.

The expense of PET scanning, and the impracticality of scanning acutely ill patients, mean that PET is likely to remain a research tool.

1.5.3 Single Photon Emission Computed Tomography

Single Photon Emission Computed Tomography (SPECT) is less expensive and more widely available than PET, but is still largely confined to research centers. SPECT may be

used to measure rCBF quantitatively using ^{133}Xe or assess regional perfusion differences using substances like HMPAO. SPECT uses either a rotating gamma camera which moves around the subject's head, or fixed position multiple detectors arranged around the head in similar fashion to a CT scanner, to acquire the image. The radiotracer may be injected intravenously (eg HMPAO or ^{133}Xe) or inhaled (^{133}Xe gas). The intensity of the emitted radiation is measured by the detectors and a computer builds the information into a cross-sectional "tomographic" map of the brain proportional to the amount of activity in each small volume element (voxel). The multipositioned detectors measure emitted rays from voxels, hopefully eliminating over- and underlying sources, with a spatial resolution of seven to twenty millimetres.¹⁸³ However problems occur due to scattered radiation.

Drawbacks are several. Firstly SPECT using HMPAO and similar compounds is similar to a microsphere technique and does not measure absolute rCBF. It can only be used to compare one side of the brain with the other, and abnormalities show up as either high flow (hyperaemia) or low flow (hypoperfusion).^{175,178} A difference of greater than 12-16% between two homologous regions of interest is required to be considered abnormal. Secondly mathematical models have been devised to describe the behaviour of the radiotracers in the brain following intravenous injection which may describe

their behaviour as accurately as possible in normal brain, but may not be true for areas of pathological brain where there is blood-brain barrier breakdown, and altered metabolism of the tracer.^{177,178} This potentially large source of error is difficult to quantify, and is the subject of considerable controversy.¹⁷⁸ Although initial uptake is proportional to flow, tracer distribution becomes a function of the partition coefficient with efflux. Imaging must be carried out soon after injection, and tracers should be used with as little efflux from the brain as possible.¹⁷⁵ With inhaled ¹³³xenon gas scatter from the nasopharynx may affect the brain images, and xenon alters cerebral blood flow by up to twenty percent in concentrations used for inhalation.^{183,184} Finally, great care is needed in performing SPECT imaging : with HMPAO and similar compounds, the injection must be given without undue disturbance to the patient, and the patient must be able to keep still for up to one hour of acquisition time. Acutely ill stroke patients are not usually this cooperative.

Several studies have evaluated the sensitivity of SPECT to rCBF abnormalities in cerebrovascular disease.¹⁸⁵ In patients with a TIA up to 60% will have rCBF abnormalities if examined within 24 hours of onset, and 40% on the second day.¹⁸⁶ In acute ischaemic stroke, SPECT demonstrates an area of relative hypoperfusion corresponding to the ischaemic tissue in most patients studied.^{175,186,187,188}

After 72 hours the relative rCBF may be increased or decreased, but enhancement on CT (thought to represent luxury perfusion) is associated with an apparent increase in relative rCBF on SPECT.¹⁸⁹ Areas of decreased rCBF in the contralateral cerebral hemisphere, ipsilateral cerebellar hemisphere and ipsilateral cerebral cortex thought to be due to diaschisis ("shut down" of areas of brain remote from the infarct) can also be demonstrated.¹⁹⁰

SPECT is a relatively cumbersome technique to use with confused and restless patients, relatively expensive tracers are used, and controversy surrounds what is actually being measured (and its accuracy) when HMPAO and associated compounds are used, so it is likely to remain a research tool for the foreseeable future.

1.5.4 Xenon Computed Tomography and Radioactive Xenon Cerebral Blood Flow Measuring Methods

Xenon is an inert gas which when inhaled, is taken up by the brain (because of its fat content). The rate of washin or washout can be used to measure cerebral blood flow.¹⁹¹ This is accomplished either by using CT to measure brain density changes (which are proportional to the xenon concentration in brain tissue) or measuring radioactivity if a xenon isotope is used.^{173,192} Xenon CT is a potentially attractive method because CT is already widely available, and consequently it has enjoyed some popularity. Many CT

scanner manufacturers now make a computer package for performing xenon CT CBF studies.¹⁹³ There are however significant drawbacks to both CT and radioisotope xenon inhalation techniques. The relatively large volumes of stable xenon required are expensive. CT scanning time is expensive - it may take up to two hours to complete a brain blood flow examination by the xenon CT method. The patient must lie very still throughout the whole period, which seriously limits its usefulness in acutely ill patients. The radiation dose is high to the brain with xenon CT and to the nasopharynx with radioactive xenon. Radioactive xenon CBF techniques cannot be repeated quickly (ie within hours) as it takes some time for the gas to wash out.¹⁹⁴ Perhaps most importantly, xenon alters CBF in animals and human subjects.¹⁹⁵ Xenon may increase or decrease CBF in normal subjects and the effect on pathological areas of brain is unknown. This could lead to large errors in comparing CBF between the two hemispheres in conditions where there is a focal abnormality such as an acute ischaemic stroke.^{183,184} Finally xenon CT and radioactive xenon techniques can only measure relative, not absolute CBF, although xenon CT does allow regional partition coefficient to be measured giving better accuracy.

Although xenon CT has been used in acute ischaemic stroke,¹⁹⁶ the above impracticalities and unquantifiable sources of error mean that its use will probably be limited.¹⁹⁷

1.5.5 First pass techniques of assessing the cerebral circulation

Stewart in 1894 described circulation time as the time taken for a variety of substances injected as a bolus to pass from the site of injection to the point of interest. He called the average time for the bolus to pass the mean transit time (MTT) and used this as an indirect measure of blood flow.¹⁹⁸

$$\text{Flow} = \text{Volume} / \text{Time}$$

Further work on this was done by Hamilton in the 1930s who was able to show that when an intravascular tracer is injected into a vein and consecutive arterial samples are taken from a point distal in the circulation, a characteristic concentration/time plot is produced (Figure 1.5.1) irrespective of the intravascular tracer used.¹⁹⁹

This plot typically has a sharp upslope as the bolus first arrives at the sample site, a rounded peak, a slower downslope to a higher point than the baseline, followed by a shallow upslope. The shallow upslope is due to recirculation. Meier and Zierler, in 1954,²⁰⁰ provided a theoretical basis to show that the flow equation applies to the cerebral circulation, but only if the tracer used remains intravascular.

Stewart and Hamilton both realised that the behaviour of the bolus was fundamental to the shape of the curve although they disagreed on what part of the bolus was the

most physiological. Stewart thought that the leading edge of the bolus, ie the fastest transit time, was most important and thought that it would not differ significantly from the mean transit time.¹⁹⁸ Hamilton argued that the mean was more important because it took account of all the vascular pathways, longest as well as shortest.¹⁹⁹ The mean is the parameter of time most commonly used today. With regard to the behaviour of the bolus, Stewart also recognised the potential errors of his method, most of which still apply to more modern ways of measuring circulation time :

- a) incomplete mixing of the indicator at the injection site
- b) problems with intravascular dispersion and recirculation
- c) pressure artifacts from the process of injection
- d) the osmotic effect of a high concentration of indicator
- e) the duration of injection and its relationship to the cardiac cycle, and
- f) the only true transit time measurable is from the start of injection, no matter how remote - the time/activity curve at the site of measurement is really a retention time, not a true transit time.

Various mathematical methods have evolved for analysing the concentration/time curve to try to minimise these sources of error. Stewart simply measured the fastest circulation time with a stopwatch. Hamilton plotted the curve, cut it out and balanced it on a knife edge to find the center of balance (method of moments) but this is only

applicable when the bolus injection is intraarterial immediately prior to the organ of study, as dispersion of the bolus invalidates it. Nylin used the shape of the curve without any mathematical analysis, and showed that under normal circumstances the curves for the two cerebral hemispheres in an individual are the same.²⁰¹ Crandall avoided the effect of recirculation by extrapolating the down slope to zero assuming it was linear.²⁰² Neither of the latter techniques offered a particularly useful or accurate interpretation of the time/activity curve.

Oldendorf, in 1960, injected an isotope into an arm vein and placed scintillation counters over each cerebral hemisphere avoiding carotid artery and jugular vein sampling.²⁰³ This made the technique less invasive but produced more dispersion of the bolus because of the longer pathway from arm to head. He estimated that, following injection into an arm vein, the bolus would have become stretched out over a five foot length by the time it reached the brain - the tail was still entering the brain as the leading edge left - and recirculation became a real problem. The resultant time/activity curve required more complex mathematical analysis. Four mathematical techniques have been tried to overcome these problems:

1. first differential of the time/activity curve
2. evaluation of the elements of the time/activity curve
3. convolution/deconvolution

4. fitting a gamma variate

The first was used by Oldendorf who calculated the maximum rate of arrival and of disappearance of tracer from the head, and assumed that the mean transit time equalled the difference. However this this did not take into account the dispersion of the bolus prior to arrival in the cerebral circulation and has subsequently been shown to measure the mode, not the mean, transit time.^{204,205}

The second was to concentrate on evaluating different aspects of the activity curve, avoiding any calculation of transit time, by calculating a) the time from injection to appearance in the brain,²⁰⁶ b) the gradient of the initial upslope,²⁰⁶⁻²⁰⁸ c) the gradient of the downslope,^{207,208} and d) time from appearance to disappearance of the isotope.²⁰⁸ However when none of these methods when subjected to clinical evaluation were found to be reproducible or reliable, and the overlap between normal and abnormal values was high.

Britton used convolution/deconvolution analysis which attempts to extrapolate an ideal time/activity curve (as if the bolus had been injected directly into the carotid artery) from the intravenous curve, and then dividing the area under the "ideal" curve by its height to calculate the mean cerebral transit time.²⁰⁹ This produced "noisy" curves so only three regions of interest over each hemisphere could be identified and a parametric image could not be produced.^{209,210}

The function called the "gamma variate" is a complex power function developed by Thomson in 1964,²¹¹ which can be used to fit experimental first pass curves effectively excluding the effects of recirculation. The gamma variate can be expressed by the formula:

$$C_t = K(t-AT)^a \cdot e^{-(t-AT)/b}$$

where

C_t = count rate at time t

K = constant

t = time after injection

AT = arrival time of tracer

a, b = arbitrary parameters.

Also the basic equation for determining the mean transit time at any point in the circulation is given by:

$$\text{mean transit time} \sim C.t / C$$

where: $C.t$ = the sum of the product of counts and time

C = the sum of the counts

But for this second equation to be applicable to the cerebral transit time method, the first pass of the bolus through the brain must be separated from the effects of recirculation. This can be done by applying the gamma variate function, but to calculate the true cerebral transit time from an intravenous injection, it is also important to exclude the effect of dispersion of the bolus prior to it reaching the brain.

Dispersion of the isotope bolus has been the most difficult factor to compensate for when determining cerebral

transit time from an intravenous injection. The bolus may become stretched to as much as five feet in length by the time the leading edge reaches the brain, and the tail of the bolus is still entering the brain as the leading edge leaves.²⁰³ Davenport in 1983 demonstrated that the number of theoretical mixing chambers through which the bolus must pass before reaching the head can be represented by $(a+1)$ where "a" is one of the arbitrary parameters in the gamma variate equation.²¹² The time taken to empty each theoretical chamber is given by "b", the other arbitrary parameter in the gamma variate equation. The mean transit time is therefore proportional to $b(a+1)$. A simpler derivation has been described by Merrick et al²⁰⁵ based on recognising that transit times are additive, that is, the time taken for the isotope to pass through each theoretical chamber (represented by the peripheral veins, right side of heart, lungs, left side of heart and aorta) is independent of the time taken to pass through each individually, but the total transit time from vein to aorta is the sum of the time taken to pass through all the chambers. It should therefore be possible to correct for dispersion of the bolus prior to reaching the head by measuring the transit time from injection to traversing the aortic arch and subtracting this value from the cerebral transit times. The fact that transit times are additive has been confirmed in an in vitro model.²⁰⁵ In practice in patients, a detector is placed over the manubri-

um sternum to detect the activity curve as the bolus traverses the aortic arch. A gamma variate function is fitted to this curve, from which the mean transit time is determined by plotting the \log^e of the fitted counts against \log^e of time.²¹³ This converts the fitted curve to a series of linear points. A linear regression fit is then applied to the graph, and the gradient of the slope is equal to "b" (one of the parameters in the gamma variate equation) while the intercept on the x axis is equal to "a" (the other arbitrary parameter). By knowing the values of "a" and "b" the mean transit time can be calculated from $b(a+1)$. The mean transit time through the aortic arch is then subtracted from the overall cerebral transit time (calculated in the same manner), having also included a correction for the time delay between the bolus leaving the aortic arch and arriving at the base of the brain. This latter is called the "arrival time". Thus the final measurement of mean cerebral transit time reflects the true transit time through the head, having corrected for bolus dispersion by subtracting the arm-to-aortic transit from the transit time measured at the vertex, and by using the gamma variate function to exclude the effects of recirculation. The "arrival time" allows delay in transit through the neck, such as might be caused by a tight carotid artery stenosis, to be identified.

1.5.6 Development of the Mean Cerebral Transit Time technique for clinical use.

The fact that transit times are additive was used to produce a "parametric" image of MCTT (and its reciprocal cerebral perfusion reserve).²⁰⁵ A "parametric" image may be read as having x, y and z dimensions that represent the parameters of time, distance and isotope concentration.

In practical terms, the subject was placed supine with the neck extended so that the vertex of the skull was placed over a small field of view gamma camera with an ultra-high sensitivity collimator. The camera was angled to exclude the trunk, and the skull positioned with the radiographic base line (ie the imaginary line joining the outer canthus of the eye to the external auditory meatus) parallel to the camera surface. A one centimeter diameter scintillation detector with a cylindrical collimator was placed two centimeters cephalad to the manubriosternal joint to view the aortic arch. The camera and scintillation detector were connected to a computer. A wide bore cannula was inserted into an antecubital vein and a suitable intravascular, non-diffusible, radioisotope tracer (such as 600 MBq of Technetium^{99m} pertechnetate, Technetium^{99m} human serum albumin, or Au^{195m}) in less than 1.5 ml of fluid was injected into a short reservoir tubing attached to the cannula. The computer was started and the isotope bolus flushed in with 10ml of saline by hand. Camera and scintillation detector images

were acquired at the rate of 10 frames per second using a 32 x 32 pixel matrix (pixel area approximately 8 x 10 mm). Figure 1.5.2 illustrates a patient correctly positioned for an MCTT study. The typical time/activity curve detected by the scintillation detector is shown in Figure 1.5.3a and a brain curve detected by the gamma camera in Figure 1.5.3b. These curves were visible on the computer screen during the acquisition so that the adequacy of the isotope bolus at the aortic arch and head could be assessed immediately. After approximately 45 seconds the isotope bolus had passed through the head and the acquisition phase was complete.

The data were then processed to produce the transit time image as follows. In the study done for this thesis, two different computers were used, one to acquire and one to analyse the data, but it would be possible to incorporate the analysis program into the acquisition computer if sufficiently powerful. A modern desktop PC (120 MB hard disk, 640k ram) would be suitable, and this would allow processing of information more quickly. To process the image, the initial spike (due to activity in the superior vena cava - see Figure 1.5.3a) was subtracted from the aortic curve by fitting a gamma variate function with manual setting of the start and end points using the computer. A gamma variate function is then fitted to the aortic curve to exclude recirculation and obtain the mean transit time from the arm to the aortic arch (MTT_{S-A}). On the brain time/activity

curve the frames corresponding to the first pass through the head were identified. After condensing to 20 frames and smoothing to improve statistical quality, a three-dimensional $32 \times 32 \times 20$ pixel matrix is produced. Pixels outside the outline of the head were set to zero, and each pixel corrected for dead time. Data points between the first rising and 70th falling fractile were identified, and MTT_{S-J} and t_a calculated for each pixel. MTT_{S-A} was subtracted and an image matrix produced of the MCTT. As discussed in 1.2.9, cerebral blood volume is proportional to cerebral blood flow multiplied by time, and cerebral perfusion reserve (CPR) is proportional to the cerebral blood flow (CBF) divided by the cerebral blood volume (CBV), which is also the reciprocal of the cerebral transit time. Thus a second image, the reciprocal of the MCTT, could be produced to show the CPR. A third image was produced representing the difference between the arrival of the bolus at the aortic arch and at each matrix point in the head (the arrival time image). The images were displayed as if looking down on the patient's vertex, with different time intervals colour-coded, interpolated to a 128×128 matrix to give a smoother picture. Faster transit times were displayed in shades of blue and slower in red, with a total of 30 shades each representing a half second difference in transit or arrival time.

The arrival time image is also displayed as though looking down on the vertex using the same colour-coded scale

and is useful because delay in transit of the bolus through the neck may indicate underlying atheromatous carotid stenosis, which could be taken into account when viewing the cerebral transit time image to improve interpreting of the likely site of arterial pathology.²⁰⁵ A normal MCTT study is shown in Figure 1.5.4. The cerebral transit time image is displayed as well as the arrival time image and the absolute values for hemispheric transit and arrival times.

1.5.7 Validation of the Mean Cerebral Transit Time technique in preliminary clinical studies

Studies in normal volunteers and "patient controls" (see below) have shown that normally isotope transit is fastest through the anterior two-thirds of the brain and slowest through the posterior third. There should be no more than one second difference between equivalent points in the two hemispheres.^{205,214} The range of normal hemispheric transit times was found to be 2.2 to 7.7 seconds, median 4.6 seconds, 95% confidence limits 2.8 to 6.2 seconds in "patient controls" (102 patients referred for brain scintigraphy who on follow up to one year were found to have no neurological or cerebrovascular disease). An MCTT longer than 6.2 seconds suggested obstruction to the flow of blood through the hemisphere.²⁰⁵ By displaying the MCTT as a parametric image from the vertex, it was possible to identi-

fy not just whole hemispheric abnormalities but also abnormalities affecting only part of the hemisphere. For example, presumed occlusion of the MCA main stem resulted in delayed transit through at least the middle two quarters of the hemisphere.²¹⁴

In the validation studies, there was no correlation of MCTT with the subject's age, although the arm-to-aortic arch transit time did correlate weakly with age (the older the subject, the slower the arm-aortic arch circulation time).²⁰⁵ Presumably this is partly due to the increasing likelihood of impaired cardiac function resulting in reduced cardiac output in older subjects. Marked impairment of cardiac function might dilute the tracer bolus in the heart invalidating the MCTT measurement, but it is not known how frequently this may occur in practice, or how important it may be clinically.

The MCTT has also been validated against TCD in normal subjects at rest, hyperventilating, and rebreathing CO₂.²¹⁴ A highly significant linear relationship was demonstrated between end tidal CO₂ and hemispheric MCTT. Also in 32 patients with first ever acute ischaemic stroke and no clinical evidence of impaired cardiac function, the MCTT predicted the site and extent of MCA occlusion accurately when compared with TCD.²¹⁵

These preliminary studies were encouraging, but to establish the true practicality of the MCTT as a diagnostic

test for the site and extent of major intracranial artery occlusion in acute ischaemic stroke requires evaluation in a more heterogeneous group of patients with coincident cardiac and carotid disease.

1.5.8 Potential advantages of the MCTT technique as a diagnostic test in acute ischaemic stroke

The MCTT is inexpensive and quick to perform, taking less than five minutes to complete the test (including insertion of the intravenous cannula), the actual imaging time during which the patient must keep still being less than one minute. A further five minutes is required for processing the image, so the final result can be obtained within ten minutes. The MCTT is not dependant on the skill or experience of the operator in the way that TCD is. It is potentially a very "user friendly" technique, ideally suited to rapid investigation of acutely ill patients who are unable to cooperate with lengthy procedures. Gamma cameras with computers are already available in many hospitals. Thus, if shown to be practical and accurate in a broader cross section of acute stroke patients, the MCTT could be a practical non-invasive vascular imaging method for diagnosing the site and extent of arterial occlusion in acute ischaemic stroke. Although at the moment there is no clinical use for this information, it may be useful in research

and in future, it may be useful to guide acute ischaemic stroke treatments if any become available, as some may be more effective in certain subgroups of ischaemic stroke.

The mean cerebral transit time and its reciprocal, cerebral perfusion reserve, are useful concepts in cerebrovascular disease as they give information on the residual capacity of the brain to cope with flow reduction, which simple measurement of CBF does not. Further assessment of the accuracy and practicality of the MCTT in the generality of patients with acute ischaemic stroke is required.

Summary of Chapter Five

1. The background history of attempts to measure CBF is described.
2. The Fick principal and Kety and Schmidt's modification is described.
3. Different clinical methods of applying the Kety and Schmidt method to measure CBF are described.
4. The development of the concept of transit time to measure blood flow is described.
5. The isotope mean cerebral transit time technique methodology and initial validation is described.

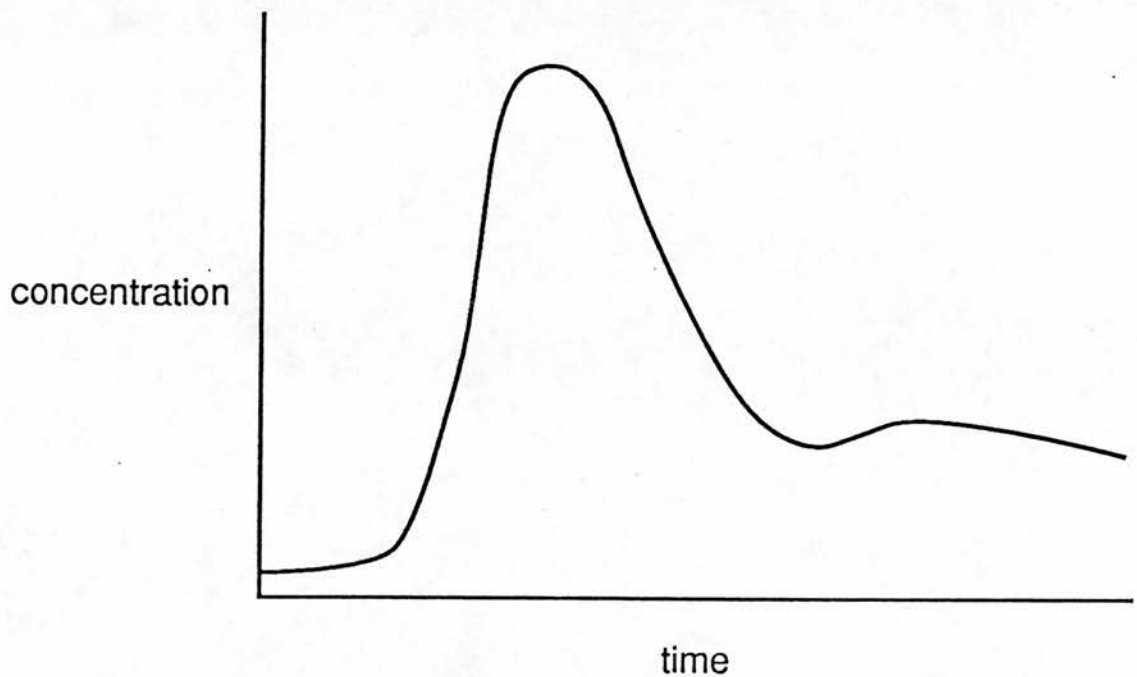


Figure 1.5.1 Graph of Concentration Against Time obtained when a bolus injected into the circulation proximally passes the point of measurement. Typically there is a sharp up-slope, followed by a rounded peak, a downslope which is less steep than the upslope, and a second lower flatter peak due to recirculation.

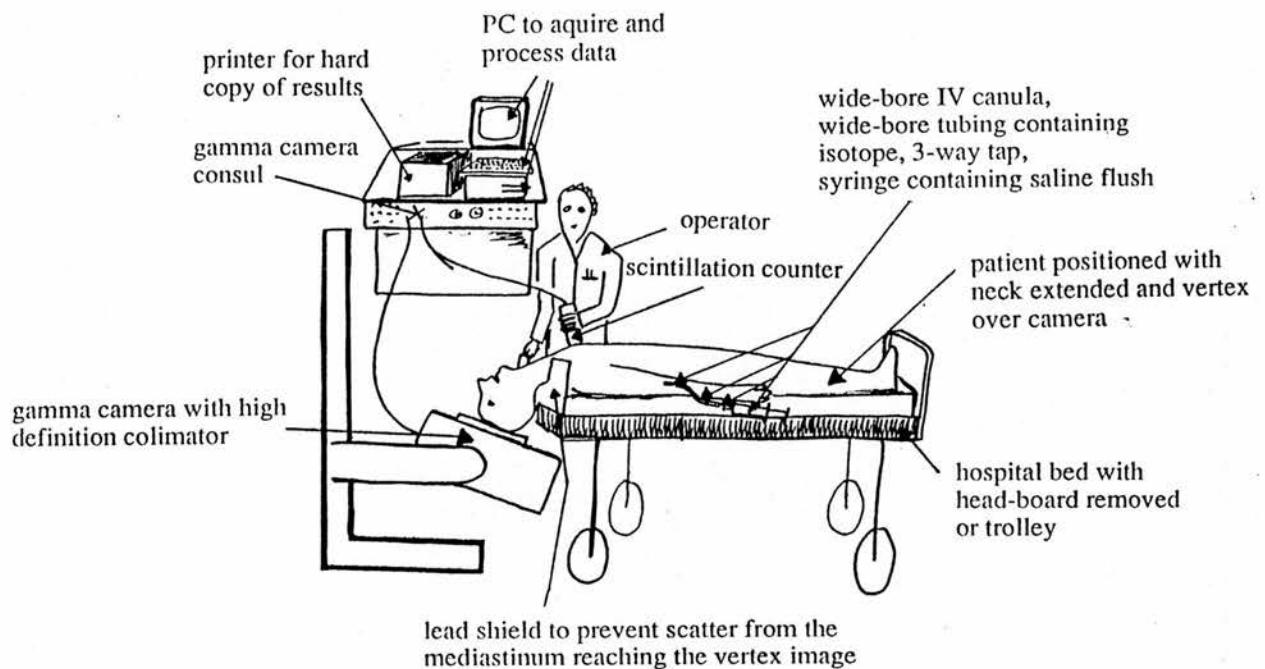


Figure 1.5.2 Drawing to show the apparatus required to perform an MCTT study, correct positioning of the patient, gamma camera and hand-held scintillation counter. With the equipment organised thus and a cooperative patient it was possible for one operator to perform the study, but otherwise two were necessary - one to steady the patient's head, the other to give the injection and operate the computer.

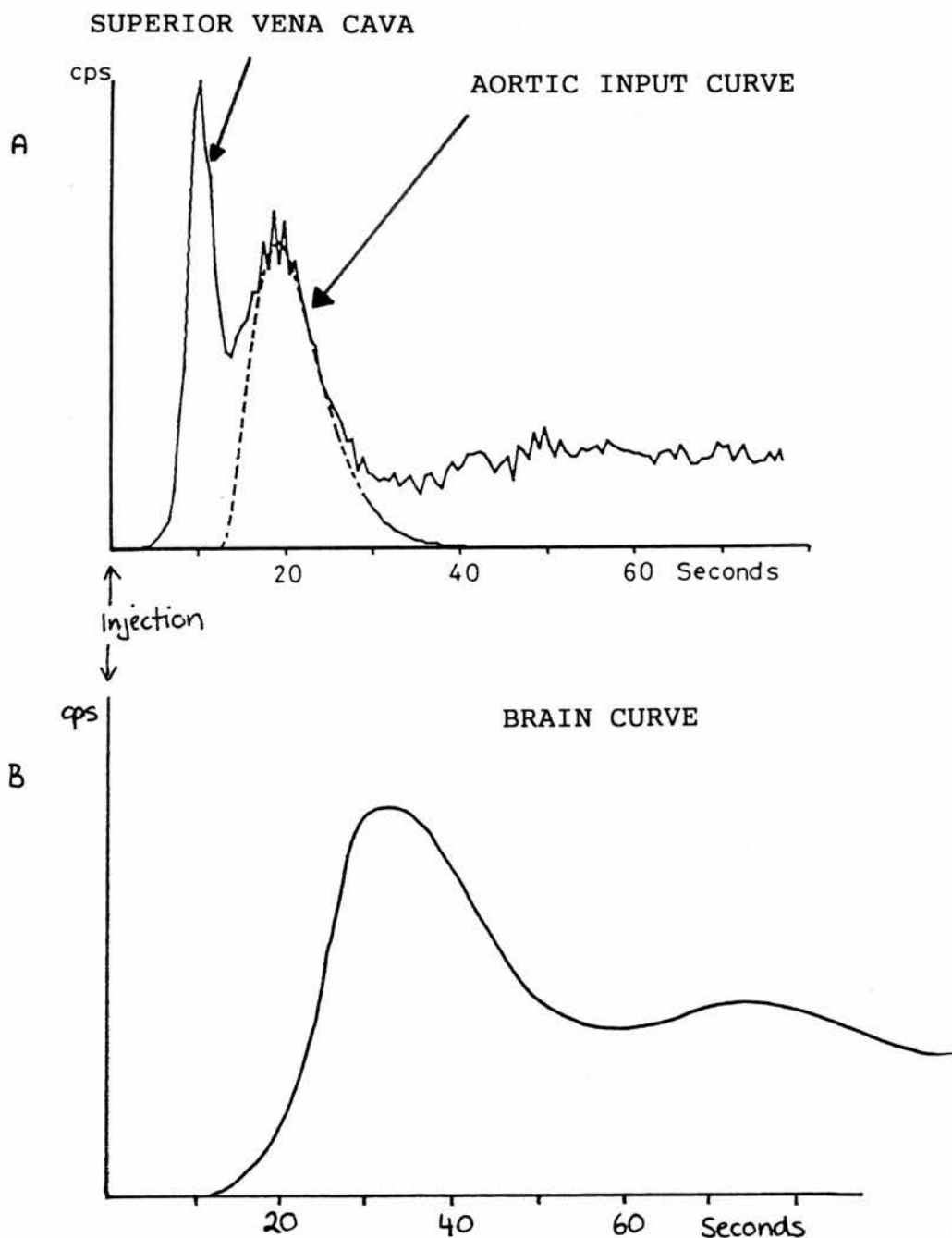
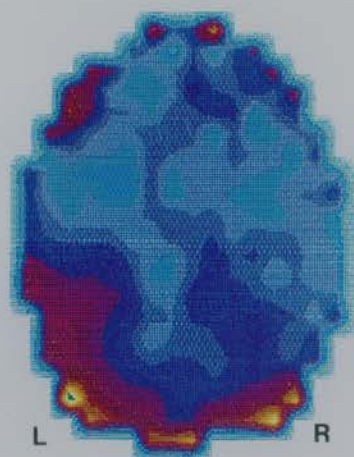


Figure 1.5.3 Typical Time/Activity Curves obtained following bolus injection of radiolabeled tracer into an arm vein. A) Measurement over the Aortic Arch : the first (sharp) peak is due to radioisotope passing through the superior vena cava; the second (blunter) peak is due to passage of radioisotope through the aortic arch. The dotted line is the "best fit" for the aortic input curve drawn by the computer. B) Measurement Over the Brain from the Vertex. CPS = counts (of radioactivity) per second.



MEAN TRANSIT TIME



ARRIVAL TIME

INPUT ARRIVAL TIME 6.4 SEC.

INPUT MEAN TRANSIT TIME 6.7 SEC.

LEFT SIDE CBF PARAMETERS

PIXELS	MTT	AT
23	5.2	3.3
33	4.4	3.3
32	5.8	3.3
29	6.1	3.3

RIGHT SIDE CBF PARAMETERS

PIXELS	MTT	AT
17	5.3	3.3
26	4.4	3.3
26	5.2	3.3

Figure 1.5.4 Example of a normal Mean Cerebral Transit Time study. Top left is the mean cerebral transit time image representing the time for the radioisotope to pass through the brain; top right is the arrival time image representing the time taken for the radioisotope to pass from the aortic arch to the base of the brain; bottom left are the absolute values for the mean cerebral transit (MTT) and arrival (AT) times in seconds for each hemisphere divided into four wedge-shaped segments. Note that the images are presented as though looking down on the top of the head (opposite to the conventional way of presenting CT scan images of the brain). Note also the colour scale consisting of thirty colour shades, each representing 0.5 seconds, blue being the fastest and yellow the slowest times. The vacant box, bottom right, may be used to present previous images of the same patient, or the inverse of the transit time image, the cerebral perfusion reserve image.

Part One

Chapter Six

Imaging the Brain Parenchyma in Acute Stroke -

Computed Tomographic Scanning and Magnetic Resonance Imaging

1.6.1 The development of CT scanning

1.6.2 CT scanning in cerebrovascular disease - cerebral haemorrhage

1.6.3 Cerebral infarction - typical appearance on CT and changes with time

The contribution of CT scanning to the understanding of the
pathophysiology of cerebral infarction and its importance :

1.6.4 Oedema and mass effect in cerebral infarcts

1.6.5 Haemorrhagic transformation of the infarct

1.6.6 Magnetic Resonance Imaging in cerebrovascular disease

1.6.7 Concluding comments

Summary of Chapter Six

1.6.1 The development of Computerised Tomographic Scanning

The invention of Computerised Axial Tomography (CT Scanning) in 1972 revolutionised clinical neurosciences.²¹⁶ It was developed by Godfrey N Hounsfield working in the Central Research Laboratories of EMI Ltd, in Middlesex, UK, who applied computer technology to detect x-rays passing through the body in cross-section and build up the transmitted x-rays into a two dimensional image of the structures through which the x-rays had passed. The image depended on absorption of the x-ray beam as it passed through the body, thus using the conventional properties of x-rays, but the computerised technique was much more sensitive than any previous methods of detecting x-rays. It became possible to differentiate between soft tissue structures such as brain parenchyma and cerebrospinal fluid (CSF) allowing direct visualisation of brain pathology. Previous neuroimaging techniques had relied on indirect evidence of disease, such as shift of vessels on angiography or ventricles on ventriculography, to diagnose mass lesions and were invasive and dangerous. The value of CT scanning quickly became obvious²¹⁷ and within a few years there were hundreds of scanners in the USA, and other radiographic equipment manufacturers had started to produce their own versions.²¹⁸ Sadly, EMI was unable to realise the potential of Hounsfield's invention, one of the major advances in medicine this century. However Godfrey Hounsfield received the Nobel

Prize in recognition of the importance of his invention. CT scanners have advanced greatly, with faster scanning times, greater image detail and use in the body as well as the head. Perhaps most importantly CT scanning has gone from being a very expensive and limited resource available to only a few lucky patients, to being available in many large District General Hospitals in the UK.

1.6.2 CT Scanning in Cerebrovascular Disease - Cerebral Haemorrhage

The earliest reports of CT scanning in cerebrovascular disease quickly showed how valuable it was for differentiating between cerebral haemorrhage and infarction (and other pathologies such as tumours) as the cause of acute focal neurological symptoms. Ambrose in 1973 stated that "in the overall investigation of cerebrovascular disease, computerised tomography will, without doubt, come to be an invaluable means of distinguishing between haemorrhage and infarction".²¹⁷ In 1974 Paxton and Ambrose²¹⁹ reported positive CT findings in 66 of 66 patients with intracranial haemorrhage and in 27 of 55 patients with cerebral infarction, and observed density changes in the evolution of the infarcted brain tissue. Acute parenchymatous haemorrhage is of higher density than normal brain parenchyma (typically about 80 Hounsfield units (HU) compared with about 35 HU for normal brain) and this density increase occurs virtually

immediately. There have been a few reports of cerebral haemorrhages observed while the patient was in the CT scanner which confirm the immediacy of the change.^{220,221} As soon as blood stops moving, its density increases to appear "whiter" on CT. This is true whether the blood is in an intraparenchymal haematoma or in an embolus in a large intracranial artery (see below).

Intracerebral haematomas exert mass effect depending on their size and site, compressing and damaging adjacent structures. If large, supratentorial haematomas may cause herniation of the temporal lobe through the tentorial hiatus and compress vital brainstem structures. The underlying cause may sometimes be inferred (spontaneous, traumatic, aneurysmal, or arteriovenous malformation) from the extent, site and distribution of blood.

The density of the haematoma decreases with time becoming isodense with brain within a few days to two weeks, and later hypodense,²²² so that on CT scans performed several months after the onset the haematoma appears as a defect of water (CSF) density. At this late stage a haematoma may look identical to an old infarct. Small haematomas become hypodense more quickly, so to be sure of differentiating a haematoma from an infarct the CT scan should be performed as soon as possible, preferably within seven days of onset.²²³

1.6.3 Cerebral Infarction - typical appearance on CT and changes with time

In the mid to late 1970's there were several reports of CT scanning in ischaemic stroke.^{219,224,225} The quality of scans was poor by today's standards: pixels were large; scan times slow; and processing algorithms less sophisticated. This limited visualisation of small infarcts and of subtle changes in the early stages of larger infarcts. Kinkel et al²²⁵ examined 111 patients admitted to hospital with cerebrovascular disease, and found that virtually all patients with a permanent neurological deficit had a defect in an appropriate area on the CT scan, whereas the patients with TIAs did not. He also noted mass effect in the early stages of large cerebral infarcts which could be confused with cerebral tumours. In 43% of patients whose CT scan showed primary intracerebral haemorrhage, the clinical diagnosis had been acute ischaemic stroke and the haemorrhage would not have been diagnosed without the CT scan. This was one of the first indications of how unreliable clinical criteria may be in diagnosing the cause of an acute cerebrovascular event. Campbell et al in 1978²²⁶ examined 141 patients admitted to hospital with acute ischaemic stroke as soon after the onset as possible and again seven days later, and compared the results with radionuclide scanning. They found that more than half of the ischaemic lesions were detected on the first CT scan, and 66% on the

second scan, compared with 58% on radionuclide scanning (the only alternative non-invasive diagnostic tool available). It was considered unusual to see changes of infarction prior to 24 to 48 hours on CT, although occasional ischaemic lesions were seen as early as three to six hours after onset.^{227,228}

Recently more subtle early signs of cerebral infarction have been described. Loss of visualisation of the insular ribbon and loss of outline of the lentiform nucleus have been reported as occurring within three hours of onset in ischaemic strokes of the basal ganglia, probably reflecting increased sensitivity of modern scanners.^{229,230} Loss of the normal grey-white matter differentiation and effacement of the overlying cortical sulci are other early signs of cortical infarction. Small infarcts probably appear later than large ones (because there is less tissue altering its density) so lacunar infarcts are less likely to show up in the first 24 hours (and sometimes not at all) than large territorial infarcts.^{231,232,233} Small infarcts in the brain stem and cerebellum are difficult to visualise with CT because of artifacts arising from the petrous bones.²²²

Another early, indirect, sign of cerebral infarction is the "hyperdense artery" sign. This is visualisation of acute large cerebral artery occlusion as an area of increased density in the main stem of the artery.²³⁴ The reliability of this sign is uncertain. It may be valid in young patients in whom the arteries tend to be less calci-

fied, but elderly patients frequently have calcified artery walls which may produce a similar appearance. In one series of acute stroke patients, the hyperdense artery sign was present in 50% of angiographically proven acute MCA occlusions.²³⁵ It has been associated with larger infarcts.²³⁶ Yang²³⁷ found the hyperdense vessel sign in only 5% of patients with acute cerebral infarction.

A typical established large artery infarct is wedge-shaped, of decreased density compared with normal brain, sharply demarcated, and occupies a recognised vascular territory.^{222,238} The presence of recent haemorrhage in the infarct produces areas of increased density relative to both normal brain and the infarcted tissue. Lacunar infarcts are less than 1.5 cm in diameter, usually rounded in shape, and are sited in the deep white matter and basal ganglia.^{24,231,232,233} Borderzone infarcts lie in the areas of the brain at the edges of the large artery vascular territories, ie in the parieto-occipital region for MCA/PCA and over the vertex for ACA/MCA borderzones.^{238,239,240} Striatocapsular infarcts are larger than lacunes and occur in the deep white matter and basal ganglia with preservation of the overlying cortex. They are thought to arise from transient occlusion of the MCA main stem (or prolonged occlusion of the MCA main stem with good cortical collaterals)^{241,242} or occlusion of multiple lenticulostriate artery origins from atheroma.²⁴³

The site of the lesion on the CT scan has been shown to correlate well with clinical syndromes.^{238,244,245,246} The middle cerebral artery territory is the most frequently involved (60%) followed by posterior cerebral artery (14%), anterior cerebral artery (5%), posterior fossa (5%), and multiple territories or borderzone in 14%.²²²

Typical evolution of the appearance of the infarct on CT scan has been described and is illustrated in Figure 1.6.1. Initially the lesion swells and becomes slightly hypodense compared with normal brain. The infarct becomes more clearly demarcated during the first few days.^{247,248} The swelling is usually maximal around the third to fifth days and gradually subsides during the second and third week (but see below).²²² The significance of visualisation of decreased density in the ischaemic tissue in the very early phase (within a few hours of onset) of acute ischaemic stroke is uncertain. It has been suggested that early visualisation of the infarct may indicate more profound ischaemia, or a worse prognosis²⁴⁹ but as yet there is no evidence to suggest that early visualisation of an infarct carries a worse prognosis than if the patient had the same neurologic deficit with no infarct visible. During the second week the infarct gradually increases in density sometimes becoming indistinguishable from normal brain - called the "fogging effect" because without close inspection even quite sizeable infarcts may be overlooked. The "fogging effect" may last

for up to two weeks, then the infarct becomes progressively more hypodense. Eventually a sharply demarcated, atrophic, hypodense defect remains.

The "fogging effect" may make the infarct impossible to see on CT scans done at this time. It is less pronounced in large infarcts but may lead to underestimation of infarct size and extent. It does not occur in all infarcts, and the rate of occurrence varies between reports. Skriver and Olsen²⁵⁰ observed it in 54% of cases scanned ten days after onset, whereas Becker²⁵¹ found it at some time in all cases examined with six consecutive CT scans within 42 days of stroke.

In large infarcts involving the cortex curvilinear bands of increased density may be seen at the cortical edge, at the junction of the lesion with white matter and within the lesion in the second and third weeks after the stroke. These correspond with areas of petechial haemorrhage seen on pathological specimens. These areas also enhance markedly when x-ray contrast is given²⁵² and are thought to correspond with areas where the capillaries are leaky, where there is blood-brain barrier breakdown and of frank petechial haemorrhage.²²⁷ Rates of occurrence of petechial haemorrhage vary between 15 and 40% in different series (also see below 1.6.5)^{62,253,254,255} presumably reflecting patient selection bias, the increasing sensitivity of CT scanners and observer variability in reporting.

Administration of intravenous x-ray contrast changes the appearance of the infarct. In the first six days it has very little effect on the appearance.^{252,256} In the second and third weeks contrast enhancement occurs frequently corresponding with the time of maximal blood-brain barrier breakdown and positivity of radioisotope scans^{227,257} The mechanism is probably a combination of blood-brain barrier breakdown, neovascularisation, and impaired autoregulation.²⁵⁸ The tendency to enhance with contrast gradually resolves, the time course being illustrated in Figure 1.6.1. Some authors have suggested that stroke patients deteriorated after intravenous contrast²⁵⁹ although the relationship was not statistically significant. It is possible that extravasation of neurotoxic contrast agents could be harmful, but the majority of patients described in their paper had large infarcts with poor prognosis in any case. In practice it is rare to need to give intravenous contrast as a diagnostic aid. Hayman et al²⁶⁰ suggested that early prominent contrast enhancement in large infarcts correlated strongly with development of massive haemorrhagic transformation later in the course of the infarct. They suggested that this was due to severe early vasogenic oedema, however most of their patients had large infarcts (with poor prognosis who were more likely to develop haemorrhagic transformation anyway²⁵⁵) and animal studies have shown that in the early phase of ischaemia, oedema is cellular in

origin and vasogenic oedema does not usually occur until several days after onset.^{261,262}

Interobserver reliability in reporting CT scans in patients with cerebrovascular disease has not been extensively studied. High levels of agreement (substantial to perfect) were demonstrated in two studies of the interpretation of CT scans in patients with dementia and stroke.^{263,264} However in one of the studies, all observers had free access to relevant clinical details so their interpretation of the CT scan may have been biased.²⁶⁴ A study by Bonke et al in which a group of neurologists and radiologists reviewed the same two CT brain scans (camouflaged by an assortment of other CT brain scans) accompanied by misleading clinical information, showed that the diagnosis of lacunar infarction did not appear to be biased by informing the observer that the patient was thought clinically to have had a stroke.²³² The lack of bias with knowledge of clinical details may have been because the study was limited, and is probably not a true reflection of the difficulties encountered in routine practice when faced with a CT scan showing multiple "holes in the brain" and generalised atrophy. The former makes the diagnosis of recent lacunar infarction difficult (it may be impossible to decide which "hole" is the relevant one unless serial scans show a new "hole" developing) and the latter makes the diagnosis of small cortical infarction difficult (when is a large sulcus actu-

ally an infarct?). Interobserver reliability in the interpretation of site of infarction, amount of swelling in the acute stage and of haemorrhagic transformation of infarcts has not been evaluated.

Contribution of CT scanning to the understanding of the pathophysiology of cerebral infarction :

1.6.4 Oedema and mass effect in cerebral infarcts

Some degree of mass effect due to infarct oedema may be observed in most larger infarcts. The mass effect manifests as compression of surrounding structures such as cortical sulci, lateral ventricle, or midline shift and tentorial herniation of the temporal lobes if severe. Swelling is usually maximal around the third to seventh day after onset and gradually resolves thereafter.^{247,248,265,266} The frequency of severe infarct swelling, the relationship to infarct aetiology, to reperfusion of the underlying occluded artery and other possible associated factors such as plasma glucose concentration at the time of the stroke have not been studied in stroke patients. From the scant information available in the literature, it seems that severe infarct swelling may occur in approximately 5% of all infarcts²⁵⁵ but there have been no large prospective studies where all patients had serial CT scanning (or post mortem) throughout

the first month after the stroke. The few serial studies which have been done concentrated on CT scanning survivors, so patients who died early were lost to the study, introducing bias.²⁵⁴ Further discussion of infarct swelling in the acute phase will be given in Part Three Chapter One.

1.6.5 Haemorrhagic transformation of the infarct

CT scanning is an excellent method with which to study the frequency and evolution of haemorrhagic transformation in cerebral infarcts. Post mortem studies in the acute stage of cerebral infarction are biased towards patients who die in the early stages of their stroke, and who are therefore more likely to have had a large cerebral infarct. The signs of haemorrhage resolve with time so that in patients dying weeks or months after their stroke it may no longer be possible to distinguish the relative contribution of infarct and haemorrhage to the residual lesion. The post mortem studies of Fisher and Adams in 1951⁵⁹ suggested that in most cases of haemorrhagic cerebral infarction the cause of infarction was an embolus (origin unspecified) which had broken up and moved distally exposing the ischaemic tissue to arterial blood pressure leading to haemorrhage. Of 373 brains with vascular occlusion (123 with presumed embolism, 89 with presumed thrombosis, and 161 of uncertain cause), 66 had haemorrhagic infarction and in 63 there was evidence of embolism as the cause of stroke. They did not

discuss the possibility that some of their infarcts with open arteries might have been venous infarcts, nor how the evidence of embolism was obtained. Venous infarcts are frequently haemorrhagic and obviously the artery to the infarcted brain would be patent. While venous infarction is unlikely, failure to recognise it may have contributed to the estimate of the haemorrhagic infarction rate in Fisher and Adam's study as well as in others since.

The idea that embolism is the cause of haemorrhagic cerebral infarction has become rather entrenched,²⁶⁷ to the point of haemorrhagic transformation being used in some studies as diagnostic of embolic (usually implied cardiac origin) stroke. Close examination of the literature on haemorrhagic transformation shows that there is rather poor evidence to support the reperfusion-haemorrhagic transformation hypothesis. As knowledge has increased, it has become clearer that one of the strongest associations with haemorrhagic transformation is simply size of infarct - the larger the infarct, the more frequent the haemorrhagic transformation.²⁵⁵ It is interesting that in 1953, shortly before Fisher and Adams⁵⁹ hypothesis became so widely publicised and accepted, Globus and Epstein⁶⁰ published results of experimental cerebral infarction in monkeys and dogs and some observations on post mortem brains from stroke patients. They observed that haemorrhage into infarcted tissue was often worse when the occluded symptomatic artery re-

mained occluded, and that the haemorrhage seemed to occur around the periphery of the infarct from collateral arterioles vasodilating to supply the ischaemic tissue and leaking. They produced massive intracerebral haemorrhages in dogs by this means, although they noted difference between the species which seemed to depend on the adequacy of the collateral supply. This alternative, but equally attractive, hypothesis has been all but forgotten and deserves further attention.

Fortunately CT scanning has offered the opportunity to study haemorrhagic transformation more systematically, but the aetiology and risk factors remain poorly understood as there have been few studies which addressed the problem in a methodologically sound manner as perhaps, until recently, CT has been a relatively scarce resource. Most of the CT studies were retrospective, based only on patients who had an initial CT scan plus a repeat CT scan, or who survived in hospital for a certain length of time. Few were prospective, none included a truly representative cross section of patients with all types of cerebral infarction (all were hospital based so were therefore biased towards patients with larger infarcts) and none systematically and successfully followed up, with a repeat CT scan or post mortem, all patients who entered the study. None of the CT studies managed to repeat CT scan all patients - some died or were discharged prior to a second scan and only patients who did

have a second scan were included in the assessment of the haemorrhagic transformation rate. If all the patients who died prior to follow up CT scanning had haemorrhagic transformation, the CT-estimated rate would have underestimated the true rate and the true clinical importance of haemorrhagic transformation of the infarct.

However, allowing for these inadequacies, CT scanning has shown that haemorrhagic transformation occurs in a range of severities from mild petechial to severe confluent haematomas, with and without symptomatic deterioration.²²⁵ The reported rate of haemorrhagic transformation, of any degree, varies in different series being between 15 and 45% for petechial haemorrhage^{254,268} and about 5% for symptomatic parenchymatous haematoma formation.²⁵⁵ Some of the wide range of reported rates of petechial haemorrhage may be due to interobserver variation in reporting, but this is less likely to affect the reporting of focal haematomas. Haemorrhagic transformation occurs in patients treated with and without anticoagulants.^{255,269,270,271} Patients with haemorrhagic transformation have continued on anticoagulant therapy without worsening of the haemorrhage or symptomatic deterioration.^{269,272} Haemorrhagic transformation may occur at any time after onset of ischaemic symptoms, from within the first 24 hours,²⁷³ to the end of the first month.^{254,255}

Risk factors for haemorrhagic transformation include large cerebral infarcts with mass effect,^{255,268,274,275}

raised blood pressure,^{61,268} and increasing age of the patient.²⁶⁸ A recent large CT series suggests that haemorrhagic transformation is equally common in presumed embolic (cardiac) as presumed thrombotic infarction,²⁵⁵ and that post mortem studies, and previous small CT series have been biased in suggesting the embolic stroke more commonly underwent haemorrhagic transformation.

There is fierce debate about the role of recanalisation. Until recently it was accepted that early recanalisation, such as might occur with spontaneous lysis of an embolus, increased the risk of haemorrhagic transformation. Several small recent studies have contradicted that, suggesting (with angiography) that haemorrhage is more common in infarcts where the artery remains occluded.

^{61,62,253,276,277,278}

Finally the role of antithrombotic drugs is controversial. Recent series have found no effect on the rate of haemorrhage with antithrombotic treatment (heparin or thrombolysis) but have suggested that when haemorrhage did occur it tended to be more extensive.^{268,276} Previous studies have suggested an increased rate as well as severity of haemorrhage with antithrombotic drugs.^{275,279,280} The true association between recanalisation, embolism, antithrombotic drug treatment and haemorrhagic transformation will hopefully be resolved by the large randomised controlled trials of thrombolytic and antithrombotic drugs in acute ischaemic stroke

which are underway at the moment (see Part Four).

1.6.6 Magnetic Resonance Imaging in cerebrovascular disease

Magnetic Resonance Imaging (MRI) became a clinical tool in the early 1980's. The equipment is very expensive, both to purchase and run, the main reason for the small number of MRI scanners in clinical use in the UK. MRI has been little used in acute ischaemic stroke. It is not a practical technique for use with acutely ill patients : the patient must be placed inside a tube-like magnet which makes access for monitoring or administering anaesthetic difficult; they must lie still for usually at least five minutes at a time. Many acute stroke patients are confused, restless and are frightened by the noise of the scanner (rather like loud machine gun fire). More recent scanners and scan sequences allow faster image acquisition, but even so, MRI will probably remain largely a research tool in acute cerebrovascular disease for the near future. The great advantages of MRI are not only its pathoanatomical cross sectional imaging properties, but its ability to perform angiography non-invasively and by diffusion and spectroscopic imaging to elucidate mechanisms of brain damage in ischaemia and response to experimental treatments.

Several studies of MRI in acute stroke have been

published recently. In addition to the above practical considerations, it is difficult to differentiate between acute cerebral haemorrhage and acute cerebral infarct in the first 24 hours.^{281,282} However MRI is much more sensitive to haemorrhage after the first week because of the paramagnetic effects of methaemoglobin. Tiny areas of haemorrhagic transformation not visible on CT may be identified which might influence the use of anticoagulant drugs in the future although at the moment there is insufficient knowledge of the risks and benefits of anticoagulants in cerebral infarcts with minor areas of (petechial) haemorrhage.²⁸³

MRI is more sensitive than CT to changes in tissue characteristics caused by cytotoxic and vasogenic oedema thus MRI should be able to detect pathological changes earlier than CT. MRI is able to detect small infarcts earlier, especially lacunes, which may not be visible on CT until the second week after onset, if at all.²⁸³ Large infarcts are often visible on CT within six hours of onset, sometimes earlier than on MRI.^{229,230,284} Transient lesions thought to be ischaemic have been described on MRI, but their true relationship to TIA's is not clear.²⁸⁴ MRI is more sensitive to small lesions in the brainstem and posterior fossa than CT as there is no interference from bone artifacts.²⁸⁵

The earliest ischaemic changes detectable with routine MRI (ie not spectroscopy or diffusion imaging) in stroke patients are loss of the normal flow void in the

symptomatic artery (within minutes of onset), swelling on T1-weighted images without signal change on T2-weighted images (three hours), signal changes on T2-weighted images (eight hours), and signal change on T1-weighted images (16 hours).²⁸⁴ Pronounced brain parenchymal cortical enhancement following intravenous gadolinium injection has been described within the first 24 hours after onset in patients with a TIA, partial arterial occlusion or isolated border-zone infarcts.^{284,286}

In the second week after infarct onset, diffuse enhancement of gyri overlying the infarct is often visible. This is thought to be due to neovascular capillary proliferation or loss of autoregulation in leptomeningeal collaterals and is visible for up to eight weeks after onset.^{281,287} It is mirrored by a similar appearance on CT scanning, attributed to areas of breakdown of the blood brain barrier corresponding with the gyriform petechial haemorrhage seen at post mortem.²²⁷ In the second to third weeks after onset some infarcts become isodense with normal brain on CT (fogging effect) and as they may have lost most of their mass effect by that stage, may be difficult to identify. Recent MRI studies have shown changes in T1 (increased signal), and in T2 (decreased signal) suggestive of diffuse haemorrhage in the second to third weeks. This effect is probably due to diffuse petechial haemorrhage from leaky capillaries, with diapedesis of red blood cells,^{283,288} and

would fit with "fogging effect" on CT, as the thinly spread red blood cells would cause a diffuse increase in Hounsfield numbers raising the low density of the lesion to that of normal brain parenchyma.

Long term effects of ischaemic stroke seen on MRI include Wallerian degeneration visible as atrophy and low density in the white matter of the brain stem²⁸⁷ and the effects of haemorrhage. As MRI is much more sensitive to chronic intraparenchymal haemorrhage, even years after it has occurred, it may be possible to differentiate between old lesions due mainly to ischaemia and those due mainly to focal haemorrhage, whereas CT will just reveal a "hole" which could have started life as either. This may prove useful in the assessment of patients presenting late (more than three weeks) after symptom onset in whom treatment with anticoagulants is being considered to exclude primary haemorrhage as the cause of symptoms. In practice it may prove difficult to differentiate old small focal haematomas from mildly haemorrhagic infarcts as more experience is acquired.

MR angiography allows the acquisition of images of blood vessels, without injection of contrast, by using the signal characteristics of flowing blood. This technique is not yet practical for acute ischaemic stroke (the patient must keep very still for the longish scanning time) but is promising for the assessment of carotid stenosis in patients being considered for carotid endarterectomy.^{289,290}

Two other ways of using information from MRI, diffusion-weighted imaging and spectroscopy, promise to be very useful research tools for acute ischaemic stroke. The technicalities are beyond the scope of this thesis, but essentially diffusion-weighted imaging uses the Brownian motion of water molecules in the brain and has demonstrated abnormalities in ischaemic tissue within fourteen minutes of onset in animal models.^{290,291} In stroke patients, initial studies have shown alteration of water diffusibility in the infarcted tissue which varied both within the lesion and with time.²⁹² The significance of these changes in relation to clinical outcome, reperfusion, etc has yet to be evaluated. Using MR spectroscopy metabolic changes in ischaemic tissue can be studied in vivo, particularly hydrogen, phosphate, carbon, fluorine and sodium metabolism.^{290,293,294,295,296} Amounts of N-acetylaspartate, creatine and phosphocreatine, choline-containing compounds, lactate and pH have been evaluated in preliminary studies in stroke patients, but it is too early yet to be certain of the significance of the changes. Perfusion imaging to examine the cerebral microcirculation can also be performed, but again, information from stroke patients so far is limited.²⁹⁰ It will be possible to study the natural history of ischaemic stroke and the response to drug treatment in vivo using these techniques.

1.6.7 Concluding comments

CT scanning is a practical accurate method of imaging structural brain abnormalities. It allows easy access to the patient and is quick, so is ideal for acutely ill uncooperative patients. Its main use in acute cerebrovascular disease is to distinguish cerebral haemorrhage from infarction, and other less frequent causes of acute neurological disturbance such as brain tumours. A standard CT brain scan gives no information about blood flow, and a negative CT brain scan does not exclude infarction as the cause of the patient's symptoms.

CT scanners are gradually being installed in most Health Districts in the UK, so will be available to most of the population. The proportion of patients with a stroke who have a CT brain is not known in the UK. In 1985, Sandercock et al suggested that a CT brain scan was justified on clinical grounds in only 25% of suspected acute ischaemic stroke patients.²⁹⁷ Now that the benefit of carotid endarterectomy and aspirin for secondary prevention is established and interest in acute treatment of stroke is increasing, the clinical justification for CT brain scanning will increase.

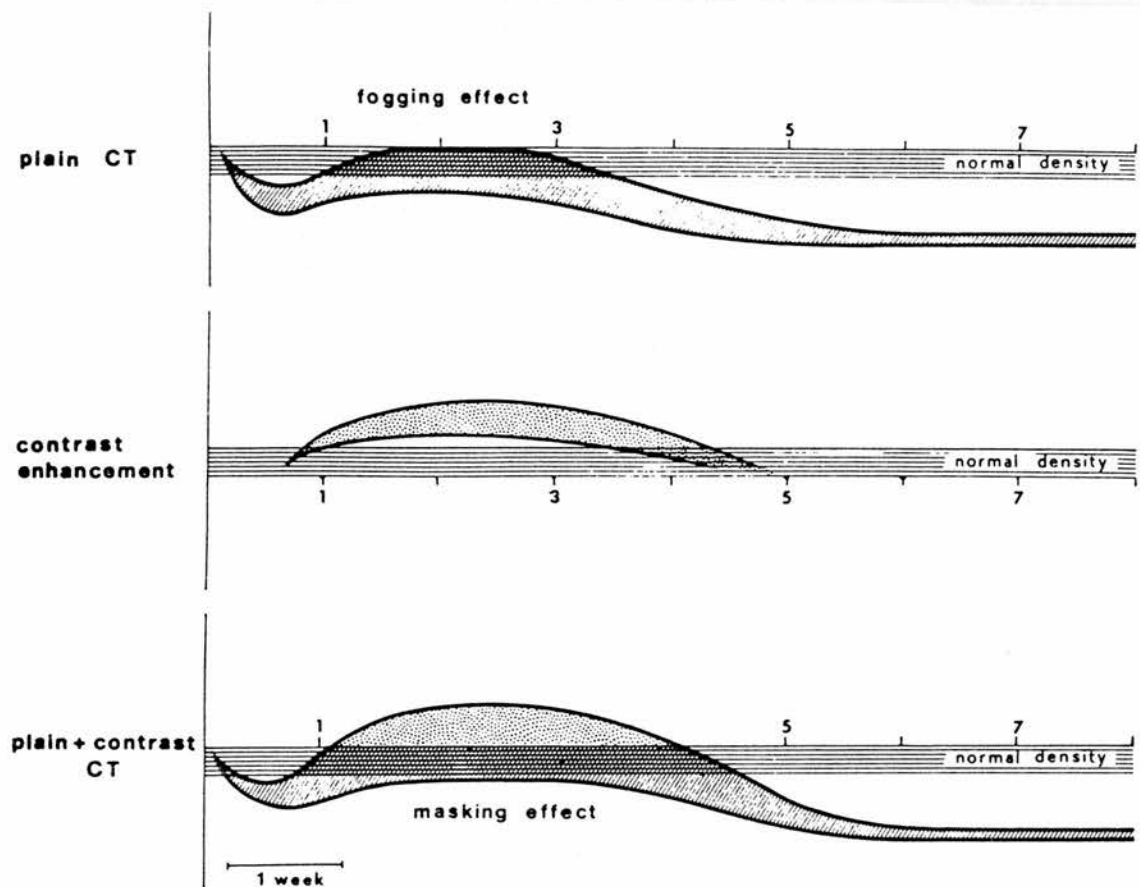
There are several important unanswered questions about acute ischaemic stroke which could be solved with methodologically sound studies using CT scanning. There are no very good studies of the frequency of haemorrhagic transformation of the infarct and the relationship to symptoms.

The significance of early infarct visibility is unclear. The proportion of patients who develop significant infarct swelling and deteriorate as a result is not known. The significance of small areas of increased density adjacent to infarcts (sometimes labeled as petechial haemorrhage) is not known. The effects of antithrombotic, thrombolytic and neuroprotective treatments on the natural history of acute ischaemic stroke are unknown. One way of answering some of these questions is by careful CT scanning (and/or MR imaging) correlated with information about blood flow patterns, and clinical features.

Summary of Chapter Six

1. The development of CT scanning is described.
2. Early studies of patients with acute stroke are described.
3. The typical appearance and evolution of cerebral infarction and primary intracerebral haemorrhage on CT are described.
4. CT scanning is an excellent diagnostic tool for acute cerebrovascular disease -it is quick, there is good access to the patient, and it differentiates easily between haemorrhage and infarction.
5. Large infarcts may be visible within a few hours of onset: many are visible by 48 hours, though some small infarcts and posterior fossa infarcts are never visualised.
6. Acute cerebral artery occlusion may be visible as a hyperdense artery.
7. The rate of haemorrhagic transformation as seen on CT scanning is discussed. The reported rates vary and the true rate may lie somewhere between 15 and 45% for petechial haemorrhage, and around 5% for large haematomas.
8. Post mortem series which examined the rate of haemorrhagic transformation were biased towards more severe strokes.
9. A brief description of MRI in acute stroke is given.

Figure 1.6.1 Evolution of the density of a cerebral infarct on CT scanning in the first five weeks after acute ischaemic stroke : y axis = density of the infarct, x axis = time. The range of normal density of brain parenchyma is shown by the group of thin lines parallel to the x axis. Typically an infarct is of low density in the first week after the stroke, then increases in density in the second week to near that of normal brain so that the infarct becomes more difficult to see (hence "fogging effect"), then declines in density from the third to fourth week onwards. Intravenous x-ray contrast raises the density of the infarct and may result in a higher density than normal brain in the second week, although the net effect of contrast may be to "mask" the visibility of the infarct if given between the second and fourth weeks after stroke onset.(222)



Summary of Part One

The history of stroke and the evolution of ideas which underlie modern concepts of acute ischaemic stroke have been outlined. A brief outline of the sequence of events in the brain following occlusion of an artery, and factors influencing cerebral blood flow have been described. All of the available neuroimaging techniques have been discussed, including the contribution each has made to improved understanding of the aetiology, pathogenesis and natural history of acute ischaemic stroke. The practical aspects of each technique (or otherwise) have been emphasised and how each might be useful to diagnose rapidly the site and extent of cerebral infarction and whether the symptomatic cerebral artery was still occluded or had recanalised spontaneously. Although the latter information is academic at the moment, if a treatment becomes available for acute ischaemic stroke, it is possible that the risk/benefit ratio may depend on the type of infarction. For example the benefit of treatment such as thrombolysis might outweigh the risks in large MCA territory infarcts where the prognosis is very poor, but not in lacunar infarcts or small MCA branch occlusions where the prognosis is much better.

Investigations should contribute as little as possible to the morbidity of the disease which they are being used to investigate. In acute ischaemic stroke it is likely that if any treatment is to work, that it will need to be

administered very quickly after onset of stroke therefore investigations should give results as quickly as possible - time delay could contribute to increased morbidity just as much as the more "direct" adverse effects of investigations (such as the one percent permanent neurological deficit following angiography).

CT brain scanning is rapid, practical, reasonably widely available, and the best way of excluding primary haemorrhage or other cause of acute neurological symptoms. However it does not give positive evidence of cerebral infarction in all cases (so cerebral infarction is a diagnosis by exclusion) and gives no information on arterial patency.

There is no perfect non-invasive imaging method to show cerebral arterial occlusion or patency. The most practical options are Transcranial Doppler Ultrasound and the Isotope Mean Cerebral Transit Time because they are inexpensive (and therefore potentially widely available), quick and cause little disturbance to the patient. All the others are expensive, slow, of little use in restless patients and not available outside specialist centres.

Further evaluation of the Isotope Mean Cerebral Transit Time technique will be described in Part Two. An investigation of the relationship between cerebral blood flow patterns, swelling in the infarct and outcome after large acute ischaemic strokes using non-invasive imaging

techniques will be described in Part Three. The setting up of a trial of thrombolysis in acute ischaemic stroke, using the information gained from Parts Two and Three, will be described in Part Four.

Part Two

Evaluation of a Rapid Non-Invasive Method of Diagnosing Cerebral Arterial Occlusion - The Comparison of Transcranial Doppler Ultrasound and Isotope Mean Cerebral Transit Time in Diagnosing the Pattern and Extent of Cerebral Arterial Occlusion in Acute Ischaemic Stroke.

Part Two

Chapter One

Evaluation of a Rapid Non-Invasive Method of Diagnosing Cerebral Artery Occlusion - The Comparison of Transcranial Doppler Ultrasound and Isotope Mean Cerebral Transit Time in Imaging the Pattern and Extent of Cerebral Arterial Occlusion in Acute Ischaemic Stroke.

Introduction

2.1.1 Aim of the study

2.1.2 Introduction and Background Information

2.1.1 Aim of the Study

The aim of the study was the further validation of the isotope Mean Cerebral Transit Time (MCTT) as a diagnostic test for patterns of cerebral arterial occlusion in patients with acute ischaemic stroke. The accuracy of the MCTT was compared with Transcranial Doppler Ultrasound (TCD) as the only practical non-invasive test of cerebral arterial patency available, using the combination of clinical examination and CT brain scanning as a "surrogate gold standard" to identify the probable site of cerebral arterial occlusion, in a broad cross section of patients with acute stroke. The intention was to devise a rapid and practical investigative imaging strategy for patients with acute ischaemic stroke with which to diagnose the likely site and pattern of cerebral arterial occlusion.

2.1.2 Introduction and Background Information

Acute ischaemic stroke is heterogeneous in its pathophysiology, including small and large artery occlusion, subcortical and cortical infarcts, embolic and in situ thrombosis. No treatment is yet available, but it is conceivable that each type of stroke might respond differently to particular forms of treatment, and that risks may vary accordingly. For example one might be prepared to offer a riskier treatment to a patient with a large infarct whose prognosis without treatment was poor, but not to a patient

with a small infarct because the latter's prognosis without treatment was so much better.²⁵ In this situation it would be important to confirm the underlying vascular pathophysiology suggested by the clinical features quickly so that treatment could commence as soon as possible. The longer the time delay, the greater the number of permanently damaged neurones and the worse the outcome. Figure 2.1.1 illustrates schematically the concept of the "ischaemic penumbra" which is now a relatively well established idea fundamental to the testing of treatments for acute ischaemic stroke.⁵¹ If all the neurones in the territory distal to an arterial occlusion died instantly no treatment to reduce neuronal damage would be possible. However it is likely that variable numbers of neurones survive for hours, possibly days in a "shut down" but recoverable state, and it is for salvage of these neurones that acute ischaemic stroke treatments are currently being tested.

In order to identify the site and extent of cerebral arterial occlusion quickly, a simple rapid non-invasive test is required. Like the ECG for myocardial infarction, it must be quick, easy to do, inexpensive, and widely available as stroke is so common. This would confirm the clinical diagnosis, and could convey information about prognosis, likely complications (for example aspiration and pneumonia in patients with extensive MCA territory ischaemia) and treatment options.

The two practical non-invasive imaging methods currently available are Doppler ultrasound (TCD) and the Isotope Mean Cerebral Transit Time (MCTT). SPECT, PET, XENON CT and MRI, as discussed in Part One, are not widely available, are cumbersome and expensive and likely to remain so, therefore will never be available to the generality of acute ischaemic stroke patients. The theory and initial validation of the MCTT has been discussed in Part One, Chapter Five.^{205,214,215} It is a simple, rapid, inexpensive, non-operator dependant test, potentially widely available as it uses inexpensive gamma camera technology. It has previously been found to be accurate in differentiating proximal MCA from small cerebral artery occlusions, but the study patients were carefully selected and few in number (only 32),²¹⁵ and its overall practicality and accuracy have not been assessed in the generality of patients with acute ischaemic stroke. The true accuracy and value of the MCTT will only be known after it has been tested in as heterogeneous a group of stroke patients as possible, including those with cardiac disease, carotid artery stenosis, and previous cerebral infarction. Anticipated problems include the possibility of non-diagnostic studies in patients with poor cardiac function (due to dispersion of the isotope bolus), and poor patient cooperation causing movement artefact making the result uninterpretable.

Transcranial Doppler ultrasound has been available

since 1982 and has been used in several published studies of acute ischaemic stroke.^{138,141,153,154,155,298,299} Training and experience are required to obtain diagnostic results with TCD and it is non-diagnostic in approximately ten percent of patients because of acoustically dense bone windows.¹²⁸ It may be less sensitive to cortical branch occlusions than the MCTT. The range of normality with TCD has been confirmed in several studies.^{128,133,138,139,157} It is a good standard against which to evaluate the MCTT. However, TCD is not a "gold standard" for the diagnosis of cerebral arterial occlusion. Its operator dependency, spatial limitations and the variability of normal cerebral arterial anatomy mean that there is a margin of error in the interpretation of TCD of uncertain magnitude. Cerebral angiography with intracarotid or vertebral injection of contrast (via the femoral route) is still the only reliable "gold standard" for delineating cerebrovascular pathology. But cerebral angiography is unpleasant for the patient, invasive, carries a small but significant risk of serious complications,^{92,93} requires patient cooperation and it is unethical as well as impractical to subject patients with acute ischaemic stroke to angiography unless for a very good reason. MRI angiography is becoming more practical but still requires cooperation and is unsuitable for use in confused, acutely ill patients without sedation. In the future, if the treatment offered to a patient following an acute ischaemic

stroke is directed by the underlying cerebral arterial pathology, then it will be important to have quick, safe methods of delineating that pathology. Cerebral angiography will never be available to the majority of acute ischaemic stroke patients, even in specialist neuroradiology centres - the number of stroke patients is too great and cerebral angiography is expensive, labour intensive and impractical. For the purpose of testing the MCTT, the pattern of cerebral arterial occlusion can reasonably be inferred from the CT brain scan (patterns of infarction resulting from occlusion at different arterial sites have been well worked out on CT²³⁸) which differentiates subcortical from cortical and posterior circulation infarction.^{238,241,242,245} Careful CT correlation of acute ischaemic stroke patients studied in the Oxfordshire Community Stroke Project (OCSF) allowed the clinical symptomatology to be matched to the vascular territory affected and the likely underlying site of arterial occlusion.^{16,25,300} When the clinical examination findings were expressed in terms of the OCSF classification as total or partial anterior, posterior circulation or lacunar infarction, the underlying pattern of cerebral arterial occlusion could be inferred. For example total anterior circulation infarction was likely to be due to proximal MCA main stem occlusion, and lacunar infarction was likely to be due to occlusion of a single lenticulostriate artery with patent large arteries.²⁵ Good correlation between the OCSF clinical

syndrome and the site of occlusion of the major intracranial arteries as shown by TCD has also been found in a small group of patients.³⁰¹ The combination of CT brain scan and clinical examination findings could therefore be used as a reliable "surrogate gold standard" for diagnosing large artery as opposed to small artery occlusion against which TCD and the MCTT could be compared. Spontaneous recanalisation of the occluded cerebral artery is known to occur - possibly up to 20% at 24 hours and up to 80% by one week after symptom onset although the frequency of recanalisation probably varies with the cause of the occlusion (embolic or thrombotic) and site (large artery or small branch occlusion).^{115,116,118,122,125} In view of this, it is only reasonable to assume that the symptomatic artery is occluded within 24 hours, possibly up to 48 hours, after symptom onset, but thereafter it will be impossible to decide from the "surrogate gold standard" which patients have recanalised. Therefore the "surrogate gold standard" is only valid within, at most, the first 48 hours after symptom onset.

It is likely that TCD, by showing increasing blood velocity in the symptomatic MCA with time after symptom onset, can demonstrate recanalisation of the basal intracranial arteries. It is not clear whether the MCTT can do this. A tracer which is intravascular as long as the blood brain barrier is intact may leak out and lead to an erroneous result in infarcted tissue where there is blood brain barri-

er breakdown. It is not clear what effect this might have on the MCTT. The previous study used ^{99m}Tc labled human serum albumin rather than ^{99m}Tc pertechnetate to avoid leakage of tracer into infarcted brain, but the former is more expensive and the latter more accessible and practical for routine use, therefore ^{99m}Tc pertechnetate will be used in this study. It could be a serious drawback of the MCTT if it were unable to demonstrate recanalised arteries in infarcted brain (as opposed to persistently occluded arteries in infarcted brain). Though suspected for some time,¹⁷⁸ the problems caused by altered behaviour of radiolabelled tracers used in SPECT scanning, notably HMPAO ("ceretec"), have recently been confirmed in stroke patients and represent a serious limitation to the use of SPECT in acute ischaemic stroke.³⁰²

Often developments - inventions, new drugs, new techniques - that are promising in the initial testing stage, prove to be impractical, unreliable or dangerous when applied in "routine" clinical practice. This study to assess the MCTT deliberately set out to be as near to "real life" as possible. The patients were as mixed a group as possible - all ages, some with previous stroke, all degrees of cardiac impairment - were included. Virtually all the TCD and MCTT studies were done by one operator as soon as possible after admission, but within practical constraints imposed by the clinical condition of the patient, availability of

porters, etc. The operator had minimal help when performing the MCTT studies, most of them were not performed in a dedicated Nuclear Medicine Department but in a side room of the Neuroradiology Department. Therefore whatever the result of this comparison, it will hopefully be directly translatable into general hospital practice.



Figure 2.1.1 The Ischaemic Penumbra. Soon after a middle cerebral artery occlusion, the neurones in the center of the vascular territory die (black area). The neurones in more peripheral parts of the MCA territory survive in a viable but "shut down" state, possibly for several hours (stippled area), though probably most of the ischaemic neurones are dead by 24 hours after onset.(51)

Part Two

Chapter Two

Evaluation of a Rapid Non-Invasive Method of Diagnosing Cerebral Arterial Occlusion - The Comparison of Transcranial Doppler Ultrasound with the Isotope Mean Cerebral Transit Time in Diagnosing the Pattern and Extent of Cerebral Arterial Occlusion in Acute Ischaemic Stroke.

Method

- 2.2.1 Study population
- 2.2.2 Clinical identification of the patients
- 2.2.3 Clinical classification of the stroke syndrome
- 2.2.4 Consent for participation in the Study
- 2.2.5 Timing of imaging studies
- 2.2.6 Imaging studies - CT brain scanning
- 2.2.7 Imaging studies - Transcranial Doppler ultrasound
- 2.2.8 Imaging studies - Isotope Mean Cerebral Transit Time
- 2.2.9 Doppler ultrasound examination of the cervical carotid arteries
- 2.2.10 Reasons for exclusion from the study
- 2.2.11 Statistical Analysis

2.2.1 Study population

The study population consisted of as many patients as possible admitted to the Western General Hospital, Edinburgh, within 24 hours of a sudden onset neurological event that was most likely a stroke, including patients with previous stroke. Patients with TIAs, subarachnoid haemorrhage, or who were disabled prior to this stroke (previous severe stroke or other cause of severe disability - Appendix 8) were not included. The study ran between the 25th November 1990 and the 31st August 1991. As this study was hospital based, the study population was biased towards more severe strokes and a higher proportion of intracerebral haemorrhages than in a community based study.^{16,300} The proportion of patients with each type of stroke was not representative of their true incidence.

2.2.2 Clinical identification of patients

All patients were examined by a physician with an interest in stroke (Dr Martin Dennis for the first six months and Dr Richard Lindley for the last three months) and their stroke clinical syndrome classified according to the Oxfordshire Community Stroke Project (OCSP) clinical classification of acute stroke (Appendix Two and see below also).²⁵

The beginning of the study coincided with an observational survey of all patients with a stroke admitted to

hospital in the North Lothian District undertaken by Dr Martin Dennis (North Lothian Stroke Survey [NLSS]). Dr Martin Dennis, Senior Lecturer in Stroke Medicine, in the Department of Clinical Neurosciences at the Western General Hospital (WGH), set up the survey to gather data on numbers of stroke patients admitted to hospital in North Lothian, type of stroke, use of investigations, inpatient care, rehabilitation and outcome, as well as patients' and relatives' opinions about the adequacy of care received. This was to provide data (there was none on stroke numbers or current care practice) on which a comprehensive stroke service for North Lothian could be based. The NLSS started on October 1st 1990 and ended on 31st May 1991. Dr Martin Dennis personally examined all strokes admitted to the North Lothian Hospitals, within 24 hours of admission, except for a few who were examined by Dr Surat Boonyakarndle, visiting neurologist from Thailand. Patients were identified by a daily round of the WGH and associated hospitals, by checking through the Casualty Department admission sheets, by direct referral once the interest in stroke became more widely known in the hospitals, and when patients were referred for CT scanning. This produced as complete a list as possible of all patients admitted to the WGH with a stroke.

After the end of the NLSS, patients were identified by Dr Richard Lindley, Research Registrar in the Department of Clinical Neurosciences. He continued to keep a list of all

patients admitted with an acute stroke to the WGH by meeting the receiving Medical Registrar every morning to find out about the previous day's admissions, and by checking the Casualty Department admissions list. He also carried a radiopager for an acute stroke treatment trial (the International Stroke Trial [IST]) and was available for advice regarding randomisation of stroke patients in the IST admitted to the WGH. Thus a complete list of all patients with an acute stroke admitted to the WGH was obtained from the 25th November 1990 until the 31st August 1991.

2.2.3 Clinical classification of the stroke syndrome

A thorough history was obtained either from the patient, close relative, or person who found the patient if they lived alone and were unable to give a history themselves. Time of symptom onset, past medical history (particularly of hypertension and cardiac disease) and drug treatment prior to the stroke were sought. If the patient awoke with the stroke the time of onset was taken to be midway between the time of going to sleep and waking. If the patient was unable to give a history, the time of stroke was deduced from a combination of the time at which the patient was found and what the patient appeared to have been doing at the time of the stroke (for example eating breakfast or getting dressed).

Hypertension was classified as "treated controlled",

"treated uncontrolled", or "untreated". "Treated controlled" hypertension was based on a statement from the GP in the referral letter or in the patient's hospital case notes from previous attendance that the patient was hypertensive and on treatment. "Treated uncontrolled" hypertension was based on the same information from the GP or case notes, but the patient's diastolic blood pressure was more than 95 mmHg (recorded by the ward nurses) at the time of admission. "Untreated" hypertension was if the patient's diastolic blood pressure was more than 95 mm Hg at the time of admission with no past history of hypertension. These categories were not intended to make the diagnosis of hypertension, but simply to be a practical and quick method of identifying possible hypertensive patients prior to performing the MCTT. Blood pressure may be elevated on admission to hospital and following an acute stroke even in patients who on follow-up are found to be normotensive. However some sort of "yardstick" was required to identify a group of patients whose MCTT might be non-diagnostic because of impaired cardiac function. Similarly evidence of previous myocardial infarction, angina, atrial fibrillation, cardiac failure or cardiac valve disease was sought, as these might be useful simple markers of impaired cardiac function.

A careful clinical examination including detailed neurological examination was performed and the patient was classified into one of the categories of stroke according to

the OCSF clinical classification of acute stroke syndromes. The OCSF clinical classification classifies all acute stroke patients into one of four clinical syndromes:²⁵

Total Anterior Circulation Syndrome (TACS)

Partial Anterior Circulation Syndrome (PACS)

Posterior Circulation Syndrome (POCS)

Lacunar Syndrome (LACS)

This is a simple classification to apply and most patients fit fairly easily into one of the categories. When used to describe cerebral infarction, the abbreviations TACI, PACI, LACI and POCI were used, the "I" indicating "infarction". The clinical features of each of the syndromes are as follows:

1) **Total Anterior Circulation Infarction (TACI)** : Patients had to have all three of a) new higher cerebral dysfunction (eg dysphasia, dysgraphia, visuospatial disorder); b) homonymous visual field defect; and c) ipsilateral motor and/or sensory deficit of at least two areas of the face, upper limb and lower limb. If the conscious level was impaired and formal testing of higher cerebral function or the visual fields was not possible, a deficit was assumed to be present.

2) **Partial Anterior Circulation Infarction (PACI)** : Patients presenting with only two of the three components of the TACI; or with higher cerebral dysfunction alone; or with a motor/sensory deficit more restricted than those classified

as a LACI (eg confined to one limb, or to face and hand but not to the whole arm).

3) **Posterior Circulation Infarction (POCI)** : Patients presenting with any of the following; ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; cerebellar dysfunction without ipsilateral long tract deficit (ie not ataxic hemiparesis); or isolated homonymous visual field defect.

4) **Lacunar Infarction (LACI)** : Patients presenting with pure motor stroke, pure sensory stroke, sensori-motor stroke, or ataxic hemiparesis. Although patients with faciobrachial and brachiorural involvement were included, those with more restricted deficits were not (these being PACIs).

2.2.4 Consent for participation in the study

The permission of the patient (or relative if the patient was unable to communicate) and the attending medical staff was obtained prior to performing the imaging studies. In many cases the CT brain scan was performed at the request of the attending physician to aid clinical management, and was not done purely for research purposes. Approval for the studies was obtained from the Lothian Area Ethics of Medical Research Subcommittee, and for the use of radioisotopes from the UK Administration of Radioactive Substances Advisory Committee (ARSAC).

2.2.5 Timing of the imaging studies

The TCD, MCTT and CT brain scans were performed as soon as possible after stroke onset, but with a maximum time lapse of 48 hours. The TCD and MCTT studies were performed at the same time if possible, but with a maximum time lapse between the two of twelve hours. Occasional patients with symptoms of extensive acute cerebral ischaemia had their first imaging study later than 48 hours (usually because of delay in admission to hospital) because these cases were of particular interest to the study of the relationship between oedema in cerebral infarcts and cerebral perfusion (see Part Three), and were included in the comparison of TCD and MCTT.

End Tidal CO₂ was measured using a Datex "Normocap 200" end tidal CO₂ monitor and a light plastic mask which fitted gently over the nose and mouth without interfering with the patient's breathing, during the TCD and MCTT studies to ensure that any discrepancy between the results was not simply due to variation in respiration.

2.2.6 Imaging Studies - CT Brain Scans

The CT brain scans were all performed in the Department of Neuroradiology, Western General Hospital, using a IGE 8800 Scanner with a fast image processing upgrade. A standard axial brain scan was performed with the patient

supine (or as near to as possible) in one centimetre slice intervals (one cm thick) from the foramen magnum to the vertex. In cases of suspected posterior fossa ischaemia additional images at 0.5 cm intervals were obtained of the posterior fossa. Intravenous radiographic contrast was not given routinely. The CT brain scans were done as soon as possible after symptom onset, preferably within 24 hours. Many patients had their CT brain scan repeated in the second week after the stroke, although this was not specified in the study protocol. The follow up CT brain scan was performed either as part of the International Stroke Trial Pilot protocol, or as part of the study described in Part Three of this thesis.

The scans were initially reviewed by myself and a simple coding system worked out for describing the site and extent of the symptomatic lesion (described below). Evidence of previous stroke was noted. Later the CT scans were reviewed blind to the clinical, TCD and MCTT information independently by myself and Dr RJ Sellar, Consultant Neuro-radiologist to assess interobserver variability in reporting of the scans, and to obtain objective and unbiased descriptions of the abnormalities.

A "recent" infarct was identified as an area of decreased density (with respect to normal brain parenchyma), usually associated with some mass effect, on the CT scan which conformed to an arterial territorial distribution as

described in Part One, Chapter Six. An "old" infarct (ie more than three months old) was identified as a well defined area of marked hypodensity with respect to normal brain (of similar density to CSF) associated with some atrophy of adjacent structures. A haematoma was identified as a rounded area of increased density with respect to normal brain, associated with mass effect.

The need for a simple classification of cerebral infarcts as seen on CT brain scans was identified because previous attempts to describe infarcts on CT brain scans have simply measured infarct volume and sometimes site.^{264,305} This conveys no information about the site or extent of the infarct or its likely clinical impact. It also does not allow separation of the extent of the infarct from the amount of mass effect caused by it or the amount of haemorrhagic transformation. The ability to separate these factors would be useful as it might then be possible to assess the impact of various therapeutic manoeuvres on the progress of the infarct, for example whether infarct swelling was altered by a particular treatment, as seen on CT. After review of about fifty CT brain scans showing cerebral infarcts (some from the patients included in this study and some from non-study patients) it became clear that the appearance of the infarcts tended to follow fairly typical and repetitive patterns. Thus it was possible to devise a classification for the appearance of the infarct on the CT

scan in which the site and extent of infarction, the amount of mass effect due to the infarct and any haemorrhage associated with it could be coded independently. The CT scan coding system is shown in Table 2.2.1. For example a typical infarct in the MCA territory might involve the posterior half of the peripheral MCA territory (cortex and white matter immediately deep to it of the posterior temporal and parietal lobes) but spare the basal ganglia and anterior half of the peripheral part of the MCA territory. Another typical though less common pattern was infarction of the basal ganglia with sparing of the overlying cortex and white matter (striatocapsular infarct). Infarcts outside the MCA territory also followed fairly repetitive patterns in the ACA, PCA and borderzone areas between the major arterial territories and in the brain stem and cerebellum. Patterns of cerebral infarction and the site of underlying arterial occlusion have been elucidated in previous studies.

238,245,303 Although some variability of vascular territories in the brain is recognised, in general patterns of infarction tend to be fairly repetitive,³⁰⁴ as arterial vascular territories are relatively consistent.

Infarcts in the MCA territory were coded from "10" to "80" according to increasing extent, "10" being a small cortical infarct and "80" being an infarct of the whole MCA territory. PCA infarcts were coded "01", ACA were "02", infarction of any borderzone was "03", cerebellar and brain

stem were "04", and lacunar infarcts were "05". Combinations of codes could be used for patients with more than one recent symptomatic infarct, for example "41" was infarction of the anterior half of the peripheral MCA territory plus the PCA territory. This classification was found to be simple to apply. Figure 2.2.1a illustrates the coding for the site and extent of the infarct, Figure 2.2.1b for the amount of swelling in the infarct, and Figure 2.2.1c for haemorrhagic transformation of the infarct. The coding for infarct swelling and haemorrhagic transformation are included here for completeness, but apply to the study described in Part Three.

Interobserver reliability for the CT infarct classification was tested using Kappa statistics following the review of all the study patients' CT brain scans independently by the author and Dr R J Sellar, blind to clinical information and classification according to the coding system illustrated in Figure 2.2.1a - c. Where there was any disagreement, discussion was held and a consensus diagnosis reached. In cases where there was still disagreement (very few) a third blinded opinion was obtained from another consultant Neuroradiologist (Dr GT Vaughan or Dr D Kean).

The accuracy of the OCSF clinical classification in predicting the site and size of the cerebral infarct on CT brain scanning was also tested. The clinical syndrome - TACI, PACI, LACI, or POCI - in the patients with infarcts

(as opposed to haemorrhages) was compared with the CT brain scan appearance of the recent infarct and the sensitivity, specificity, positive and negative predictive value and accuracy of the OCSF classification calculated. Table 2.2.2 shows the clinical syndromes and the types of infarction shown on the CT scan which were considered to be compatible. A large MCA territory infarct involved the whole of the cortex and adjacent white matter, plus part or all of the basal ganglia supplied by the MCA ("60" to "80") and was considered compatible with a TACI. A medium-sized MCA territory infarct involved about half of the cortex and adjacent white matter supplied by the MCA but spared the basal ganglia ("40" to "50") and was considered compatible with a TACI or a PACI. A small cortical infarct involved only a small area of cortex, ie less than one quarter of the whole cortex supplied by the MCA ("10") and was compatible with a PACI. A large subcortical infarct (striatocapsular - "20" or "30") was considered compatible with a TACI or a PACI. Medium-sized cortical and large subcortical infarcts were considered to be compatible with the clinical diagnosis of either a TACI or a PACI because clinically there is a grey area of overlap between the two syndromes - the exact distinction is probably not important - a PACI which is nearly severe enough to be a TACI and a true TACI both indicate significant cortical or subcortical damage. Small subcortical infarcts ("05") were considered compatible with a LACI.

Infarcts in the territory of the PCA, brain stem or cerebellum were considered compatible with a POCI. Patients with a PACI or LACI clinical syndrome and a borderzone infarct on the CT scan were classified as "borderzone PACI" or "borderzone LACI". Patients whose CT scan did not show a recent infarct (ie CT negative) were considered to be "unconfirmed" PACI, LACI or POCI depending on the clinical syndrome.

The CT brain scan and clinical examination findings were then combined to be used as the "surrogate gold standard" for assessment of the probable pattern of cerebral arterial occlusion, against which TCD and MCTT could be assessed. If the clinical examination and CT brain scan findings were in agreement, then the "gold standard" was acceptable. However if the clinical diagnosis differed from the CT brain scan, for example clinical examination suggested a lacunar syndrome and the CT brain scan showed a recent small cortical infarct but no lacunar infarct, then the CT brain scan diagnosis was taken to be correct. In patients whose CT brain scan failed to show a recent infarct the clinical diagnosis was used prefixed with the qualification "unconfirmed" for example "unconfirmed LACI".

2.2.7 Imaging Studies - Transcranial Doppler (TCD)

TCD was performed using equipment mounted on a standard National Health Service tea trolley which could be taken to the patient, thus reducing time delays. An Eden Medical

Electronics (EME) TC 64B machine with a hand held 2MHz probe was used. Beam intensity was kept at the minimum level at which satisfactory Doppler signals could be obtained. For each patient both ACAs, MCAs, and PCAs were insonated through the temporal bone windows, and the ophthalmic arteries and carotid siphons through the orbits routinely, as described in Part One Chapter Four. The vertebral arteries were insonated from the posterior auricular approach, and the basilar artery through the foramen magnum in occasional patients but not routinely.

The MCA was insonated from its origin to the M2 segment by altering the focus of the beam from 65 to 35 mm depth. The ACA was insonated at 65 to 75 mm depth, and the PCA from 60 to 80 mm depth, at which point it was often possible to record the bidirectional signal from the tip of the basilar artery.

The TCD studies were done as soon as possible after admission of the patient (within a maximum of 48 hours of stroke onset), as blind as possible to the clinical state of the patient, only the stroke patient's name and ward being known. The TCD studies were often done at the patient's bedside, with the patient supine. The TCD result was written down on the patient's study record sheet prior to finding out the clinical examination findings or the CT scan or MCTT results.

As the blood velocity in the intracranial arteries

varies with age, blood pressure, haematocrit, 128,133,144,145,146 and possibly position of the patient, the absolute value of the blood velocity in the symptomatic artery is not very meaningful. It is more useful to record the velocity in the symptomatic artery as a proportion of the velocity in the asymptomatic artery.^{138,139} A simple coding system was devised as a way of expressing this in a ranked scale, shown in Table 2.2.3. This coding allowed the pattern of each patient's intracranial blood velocity to be described with a simple three digit number that stated the degree of reduction in the MCA flow velocity on the symptomatic side (first digit), the adequacy of collateral flow to the MCA territory from the ACA and PCA (second digit), and the likelihood of ICA disease in the neck by identifying reversed direction of flow in the ophthalmic arteries and the ACA (third digit). The symptomatic MCA blood velocity had to be reduced by at least 25% of the value on the asymptomatic side to count as a reduction (or increased by more than 25% to count as an increase) and reduction by further 25% increments used to indicate further degrees of reduction in symptomatic MCA blood velocity.¹³⁸ Similarly the ACA and PCA blood velocities had to be increased by at least 25% of the value on the asymptomatic side to count as an increase, although it should be noted that there is greater side to side variation in the ACA and PCA velocities due to greater anatomical variation than in the MCA's.

The three digit code facilitated comparison with the pattern of cerebral arterial occlusion suggested by the MCTT (discussed below) and with the combined "gold standard" of the clinical examination and CT brain scan findings. For example a "600" (normal MCA blood velocities) would be compatible with a lacunar infarct or a small MCA cortical infarct (small PACI) or a POCI; a "500", "400" or possibly a "300" (indicating decreased blood velocity in the symptomatic MCA) would be compatible with a medium sized MCA cortical infarct (PACI or TACI); and a "300", "200", "100" or "000" would be compatible with a large MCA cortical infarct (TACI).

2.2.8 Imaging Studies - the isotope Mean Cerebral Transit Time (MCTT)

The MCTT studies were done according to the method described in Part One, Chapter Five. ^{99m}Techetium Pertech-netate (600MBq) was used as the tracer. The studies were done in either the Department of Nuclear Medicine just above the hospital Admissions area, or in the Department of Neuro-radiology. Studies acquired in the Department of Neuroradiology were saved onto a floppy disc, taken to the Department of Nuclear Medicine, and transferred into the computer system for analysis and storage of data. The MCTT studies done in the Department of Neuroradiology were all done by myself, occasionally with the assistance of the nurse accom-

panying the patient (who had no radiographic or nuclear medicine training). In the Nuclear Medicine Department the MCTT studies were done by radiographers trained in the technique and occasionally myself. The computer processing of the studies was done by the radiographers, Dr MV Merrick, one of the Nuclear Medicine registrars (radiology trainees) or myself. The MCTT studies were interpreted blind to the patients' clinical details, TCD or CT brain scan results by Dr MV Merrick and myself. The MCTT studies were done as soon as was possible and practical after symptom onset, as close to the TCD study as possible but within a maximum of twelve hours of the TCD study..

The result of the MCTT study was presented as a colour coded two dimensional image of the arrival time of the isotope in each pixel of a 32 by 32 matrix image, and the transit time through each pixel with a different colour shade for each half second time difference. A normal example is shown in Figure 1.5.4. A numerical value for arrival and transit times in seconds for each hemisphere divided into four "boxes" was also presented (Figure 2.2.2a). This division of the brain image into rectangular boxes appeared unphysiological so the processing program was rewritten (by Colin Ferrington, physicist) so that the brain image was divided into eight "pie" segments (four per hemisphere) approximately reflecting the territories of the MCA, ACA, and PCA as viewed from the vertex (Figure 2.2.2b). To obtain

the segmental arrival and transit time values, all the studies were reprocessed (by myself) and the values obtained by the "box" and "pie" methods compared with the absolute blood velocities obtained by TCD for each intracranial artery to see which gave the best match.

In normal subjects there should be no more than one second difference in arrival and transit times between equivalent parts of the hemispheres.^{205,214} Thus the right and left frontal, parieto-temporal and occipital areas should have arrival and transit times which differ by no more than one second (ie two colour shades). More than one second difference indicated a delay in arrival or transit in part or all of the hemisphere depending on how much of the hemisphere was affected. Transit through the front two thirds of the hemispheres was normally faster by one to two seconds than transit through the posterior one third. Loss of this normal "anteroposterior gradient" of transit time may indicate bilateral internal carotid artery stenosis or occlusion in the neck, bilateral hemispheric infarcts, or possibly that the study was flawed technically. The range of normal transit times has been shown to be between 2.2 and 7.7 seconds (median 4.6 seconds).²⁰⁵ Note that the range of normal was established, not in normal volunteers, but from a subgroup of 102 patients selected from over 2000 referred for routine brain scintigraphy, who on follow up at one year were confirmed as having no neurological disease. In the

present study a transit time for the whole head above the upper limit of the normal range was considered to be "generally prolonged" but note that the anteroposterior gradient and right to left symmetry could still be preserved despite this.

The MCTT studies were coded for comparison with TCD using the transit abnormality on the symptomatic side expressed in terms of the asymptomatic side as shown in Table 2.2.4. The transit time pattern could be described in a simple ranked three digit code, in similar fashion to the TCD codes for blood velocity. The first digit described prolongation of the transit time in the symptomatic hemisphere with respect to the asymptomatic side, "6" being normal and "2" indicating prolongation of the transit affecting the whole of the symptomatic hemisphere. The second digit described the amount of difference in seconds between the two sides (ie one to two, or more than two seconds) or whether the transit time was generally prolonged. The third digit described loss of the normal anteroposterior gradient. Thus an MCTT code of "200" implied occlusion of the MCA main stem or terminal ICA and would be compatible with a TCD code of "200" to "000", a CT brain scan showing infarction of most of the MCA territory and a TACI clinical syndrome. An MCTT code of "500" implied a peripheral MCA branch occlusion and would be compatible with a TCD code of "500" to "300", a CT brain scan showing a small to medium cortical infarct in

the MCA territory and a PACI clinical syndrome. A normal pattern ("600") would be compatible with a normal TCD examination and a lacunar infarct; a "600", "500" or "400" would be compatible with a PACI, a "400", "300" or "200" with a TACI, and a "600" or "500" with a POCI. Thus the pattern of cerebral arterial occlusion shown by the MCTT could be compared with the pattern shown by TCD, and both with the combined "surrogate gold standard" of CT brain scanning and clinical examination findings. For analysis, both codes and absolute values of transit time and arterial blood velocity were used.

2.2.9 Imaging Studies - Doppler ultrasound examination of the carotid and vertebral arteries in the neck

Duplex ultrasound (combined B mode imaging and continuous or pulsed wave spectral Doppler) of the cervical carotid and vertebral arteries was performed on as many patients in the study as possible within one week of the stroke. In most cases this was possible, but patients who died or were discharged soon after the stroke, or were too restless to obtain a satisfactory result, were omitted. The examination was done to identify significant carotid disease to aid retrospective interpretation of the TCD and MCTT. Occasional studies were done at the request of the attending clinician.

A maximum peak systolic blood velocity greater than

1.2 ms⁻¹ in the ICA was taken to indicate approximately 50% stenosis, and greater than 3 ms⁻¹ to indicate approximately 80% stenosis, combined with appropriate B mode imaging findings. Occlusion of the ICA was diagnosed when no Doppler signal could be obtained from the ICA and correct positioning of the sampling cursor was confirmed by B mode imaging.

2.2.10 Exclusions

Some patients were later excluded from analysis when further investigation showed the symptoms to be due to a condition other than stroke, eg tumour. On a few occasions the medical staff caring for the patient, or the relatives refused permission to move the patient for a CT brain scan or MCTT study, or the patient died before a CT brain scan or MCTT study could be performed. Some patients were initially misdiagnosed as a condition other than stroke, and by the time the correct diagnosis was made, several days had passed. Patients admitted on a Friday afternoon, or on Saturday but whose symptoms had begun on Friday or Thursday, and were not identified until Monday, were excluded because the time delay to imaging was too long.

2.2.11 Statistical Analysis

The clinical and imaging data for each patient were entered into a database (dBase 4) and analysed using the Statistics Package for the Social Sciences program (SPSS/PC)

using formulae for nonparametric data. Previous studies have shown that the MCTT data are not normally distributed.

205,214 Analysis of patient characteristics, eg drug treatment, cardiac history, etc was done by hand using a Chi squared test. The interobserver variability (Kappa) tests were done by hand according to the method of Sackett, Haynes and Tugwell.^{306,307}

Table 2.2.1 Coding for the CT brain scans in patients with acute ischaemic stroke

a) Site and extent of lesion (refers only to recent lesions ie likely to be symptomatic)

00 normal (includes age-appropriate atrophy, and generalised periventricular lucency)

infarcts in the MCA territory :

- 10 small cortical infarct in the MCA territory
- 20 infarct involving most of the basal ganglia (larger than 1.5 cm diameter - striatocapsular)
- 30 infarct in the white matter lateral to the lateral ventricle (larger than 1.5 cm diameter - also striatocapsular but nearer to the vertex)
- 40 infarct of the front half of the peripheral MCA territory excluding the basal ganglia
- 50 infarct of the posterior half of the peripheral MCA territory excluding the basal ganglia
- 60 infarct of the whole of the peripheral MCA territory not including the basal ganglia
- 70 infarct of the whole of the peripheral MCA territory plus the lateral part of the basal ganglia
- 80 infarct of the entire MCA territory

infarcts outside the MCA territory :

- 01 infarct of part or all of the PCA territory
- 02 infarct of the ACA territory
- 03 borderzone infarct (MCA/PCA, or MCA/ACA)
- 04 brainstem or posterior fossa infarct
- 05 lacunar infarct (small subcortical infarct less than 1.5 cm diameter)

other :

- 90 primary intracerebral haemorrhage - site indicated by code as for infarcts

Infarcts at more than one site were indicated by combining the codes, for example "11" = small cortical MCA infarct plus PCA infarct.

Table 2.2.1 continued

b) Definition of the amount of swelling of the infarct

0	no swelling
1	effacement of the sulci overlying the infarct
2	1 + slight compression of the ipsilateral lateral ventricle
3	complete effacement of the ipsilateral lateral ventricle
4	effacement of the ipsilateral lateral and third ventricles
5	shift of the midline structures away from the infarcted side
6	effacement of the basal cisterns

(swelling causing midline shift but incomplete effacement of the ipsilateral lateral ventricle was coded "5")

c) Definition of the amount of haemorrhagic transformation of the infarct

0	none
1	petechial haemorrhage (minor punctate areas of blood density (approx 60 to 80 Hounsfield Units) at the margins of or within the infarct)
2	small confluent haematoma < 2 cm in diameter within the infarct
3	haematoma > 2 cm in diameter

Table 2.2.2 Appearance of the infarct on the CT brain scan and the clinical diagnoses which were considered to be appropriate to that appearance. "Small", "medium" and "large" cortical infarcts are described in the methods. "Large subcortical" infarct = striatocapsular infarct ("20" or "30" in the CT infarct classification); "small subcortical" infarct = lacunar infarct ("05" in the CT infarct classification).

CT Brain Scan Appearance	Clinical Diagnosis
large cortical infarct in the middle cerebral artery territory	TACI
medium-sized cortical infarct in the middle cerebral artery territory	TACI or PACI
small cortical infarct in the anterior or middle cerebral artery territory	PACI
large subcortical infarct	TACI or PACI
small subcortical infarct	LACI
cortical infarct in the posterior cerebral artery territory	POCI
brainstem or cerebellar infarct	POCI

Table 2.2.3 Codes for describing the likely pattern of cerebral arterial occlusion suggested by TCD in patients with acute ischaemic stroke

primary codes describing the symptomatic MCA blood velocity:

- 700 symptomatic MCA blood velocity 25% greater than asymptomatic (ie hyperaemia)
- 600 symptomatic MCA blood velocity = asymptomatic
- 500 symptomatic MCA blood velocity = 50-75% (ie more than 25% reduction) of the asymptomatic blood velocity
- 400 focal high velocity in the symptomatic MCA with decreased velocity superficially (ie focal stenosis)
- 300 symptomatic MCA blood velocity = 25 to 50% of the asymptomatic blood velocity
- 200 symptomatic MCA blood velocity less than 25% of asymptomatic blood velocity
- 100 absent symptomatic MCA blood velocity
- 000 absent symptomatic MCA and ACA blood velocity

secondary codes describing collateral flow via the ipsilateral ACA and PCA

(to be used in conjunction with primary) :

- 010 increased blood velocity ACA on symptomatic side (by 25% more than asymptomatic side)
- 020 increased velocity PCA on symptomatic side (by 25% more than asymptomatic side)
- 030 increased velocity both ACA and PCA on symptomatic side

tertiary codes describing collateral pathways suggesting ICA disease proximal to the skull base

(to be used in conjunction with the primary) :

- 001 reversed direction of flow in the ACA on the symptomatic side
- 002 reversed ophthalmic artery flow on the symptomatic side
- 003 reversed ACA and ophthalmic artery flow on the symptomatic side

Table 2.2.4 Codes for describing the likely pattern of cerebral arterial occlusion suggested by the MCTT in patients with acute ischaemic stroke

primary codes describing abnormalities in the symptomatic hemisphere:

- 700 transit time on the symptomatic side faster than on the asymptomatic
- 600 transit time on the symptomatic side = asymptomatic
- 500 transit time prolonged in the posterior half of the symptomatic side
- 400 transit time prolonged in the middle half of the symptomatic side
- 300 transit time prolonged in the anterior half of the symptomatic side
- 200 transit time prolonged in the entire symptomatic hemisphere

secondary codes describing the amount of transit time difference in seconds in the area described by the first digit:

- 020 1 - 2 second difference
- 010 2 or more seconds difference
- 030 bilaterally prolonged transit (more than 7.6 seconds in both hemispheres)

tertiary code suggesting ICA disease proximal to the skull base :

- 001 loss of the normal antero-posterior gradient

The normal range of hemispheric transit time was 2.5 to 7.7 seconds, with no more than one second difference between equivalent parts of the hemispheres. Transit time was normally faster in the anterior 2/3 to 3/4 of the brain than in the posterior 1/3 to 1/4, therefore loss of the normal anteroposterior gradient indicated that the transit time posteriorly equalled that anteriorly.

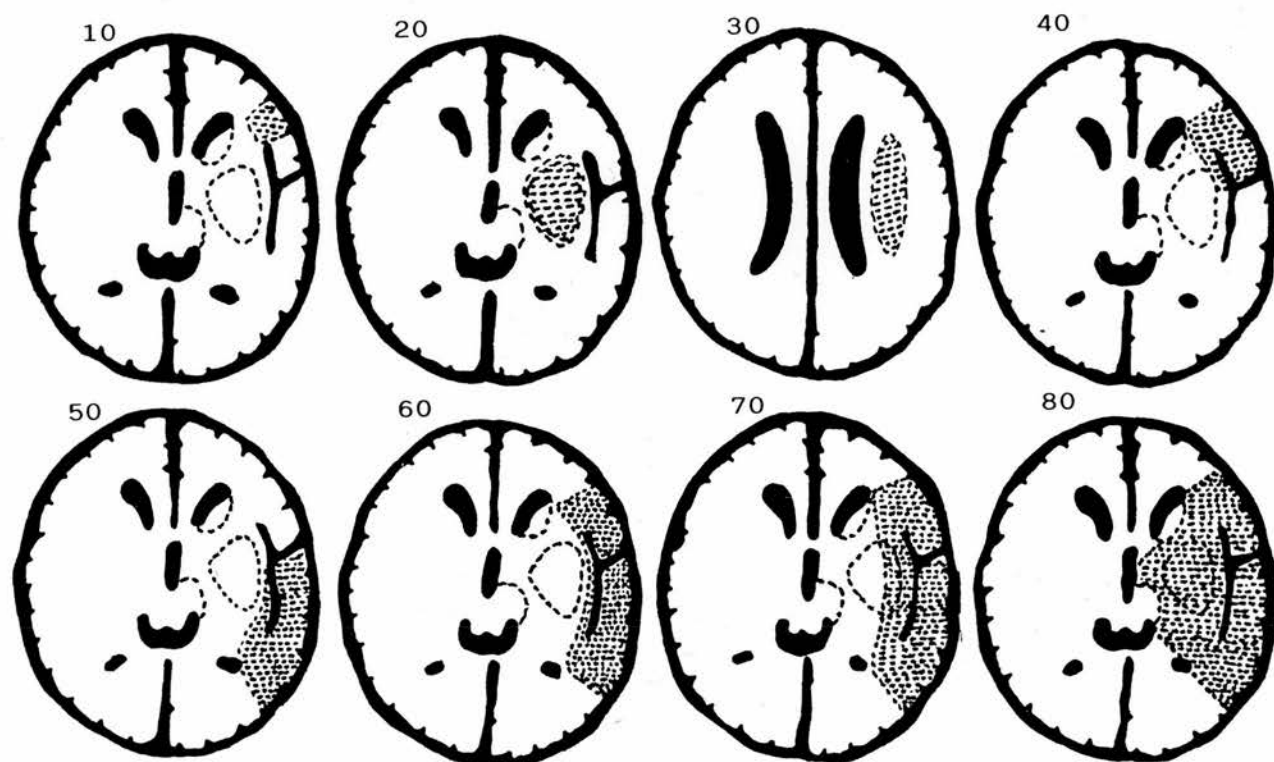


Figure 2.2.1 A : Templates for the coding used to describe the site and extent of the recent cerebral infarct on the CT brain scan - i) middle cerebral artery territory infarcts. 00 (not shown) = no infarct visible, 10 = small cortical infarct, 20 = basal ganglia infarct ($>2 \times 2 \times 2$ cm), 30 = infarct of the white matter lateral to the lateral ventricle ($>2 \times 2 \times 2$ cm), 40 = infarct of anterior half of the peripheral MCA territory, 50 = infarct of the posterior half of the peripheral MCA territory, 60 = infarct of the whole of the peripheral MCA territory, 70 = 60 + infarct of lateral part of basal ganglia, 80 = infarct of whole of MCA territory.

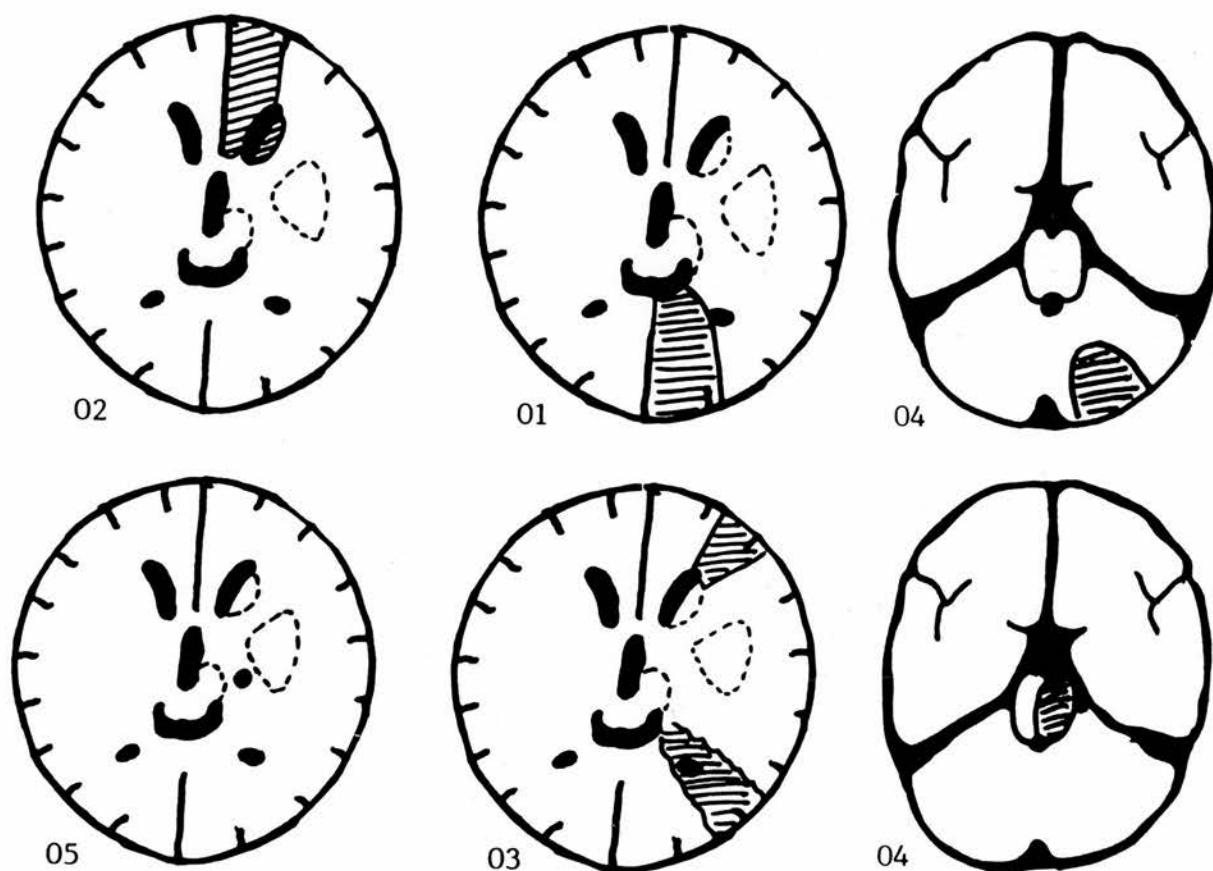


Figure 2.2.1 A : Templates for the coding used to describe the site and extent of the recent cerebral infarct on the CT brain scan - ii) anterior and posterior cerebral arteries territories, cerebellar and lacunar infarcts.

02 = anterior cerebral artery, 01 = posterior cerebral artery territory (part or all of), 04 = cerebellar or brain stem infarct, 05 = lacunar infarct (< 1.5 cm in diameter), 03 = borderzone infarct (MCA/ACA, or MCA/PCA).

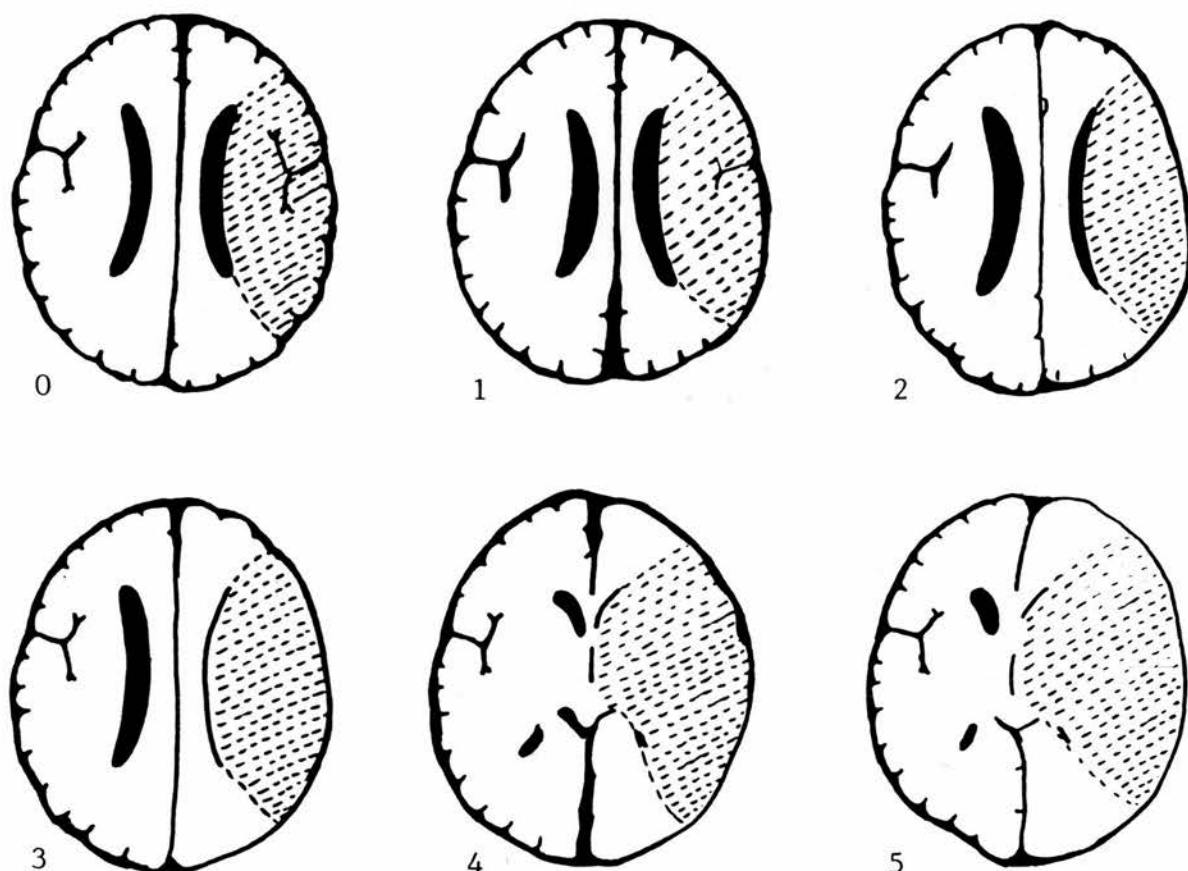


Figure 2.2.1 B : Templates for the coding used to describe swelling in recent middle cerebral artery territory infarcts on the CT brain scan. The shaded area indicates the infarct. 0 = no swelling, 1 = effacement of the sulci overlying the infarct, 2 = 1 + minor effacement of the adjacent lateral ventricle, 3 = 1 + complete effacement of the lateral ventricle, 4 = 1 + effacement of the lateral and third ventricle, 5 = 4 + shift of the midline away from the side of the infarct, 6 (not shown) = 5 + effacement of the basal cisterns. Swelling causing midline shift but incomplete effacement of the ipsilateral lateral ventricle was coded "5".

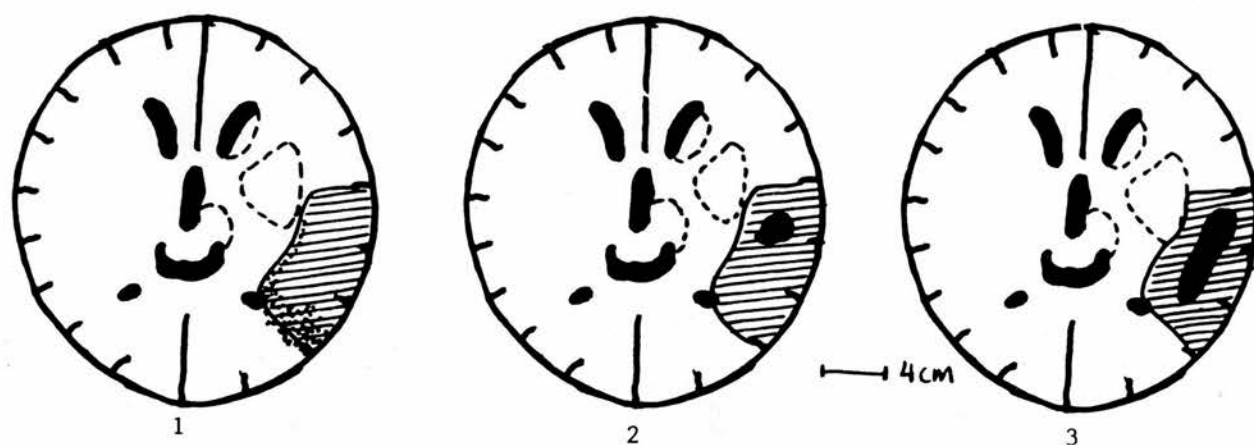


Figure 2.2.1 C : Templates for the coding used to describe haemorrhagic transformation of the recent infarct on the CT brain scan - any arterial territory. The shaded area indicates the infarct and the solid black area the haemorrhage. 0 = no haemorrhage, 1 = minor petechial haemorrhage, 2 = small haematoma < 2 cm in diameter, 3 = haematoma > 2 cm in diameter.

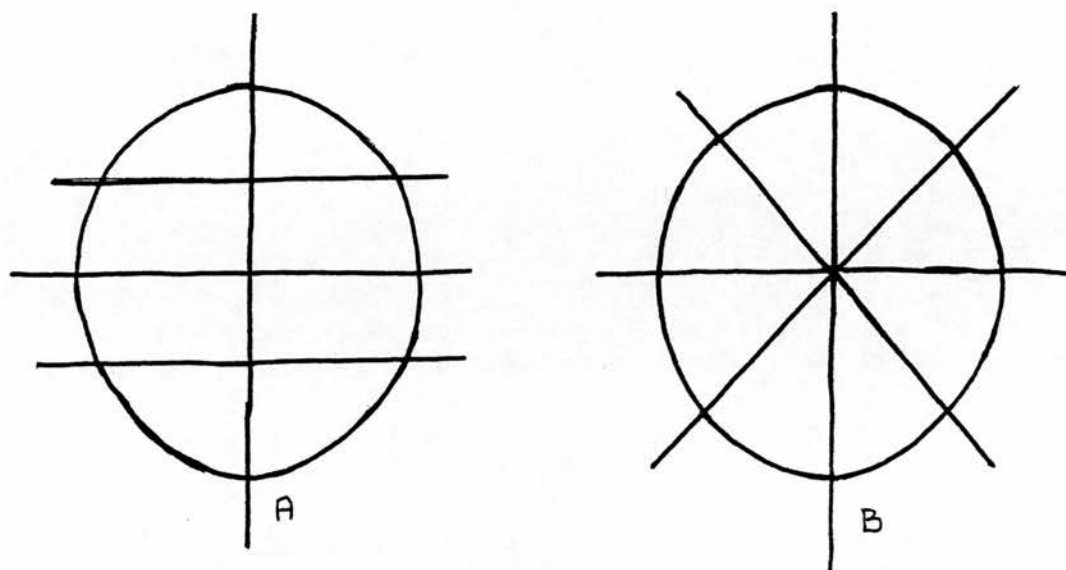


Figure 2.2.2 Method of dividing the image of the cerebral transit time into (A) boxes, or (B) wedge shaped "pie" segments to examine for regional transit abnormalities.

Part Two

Chapter Three

Evaluation of a Rapid Non-Invasive Method of Diagnosing Cerebral Arterial Occlusion : Comparison of Transcranial Doppler Ultrasound with the Isotope Mean Cerebral Transit Time in Diagnosing the Pattern and Extent of Cerebral Arterial Occlusion in Acute Ischaemic Stroke

Results

2.3.1 Study population

2.3.2 Study patient characteristics

2.3.3 CT brain scanning results including:

- a) the interobserver reliability of the CT infarct classification, and
- b) the accuracy of the OCSF clinical classification of acute ischaemic stroke in predicting the site of infarction as seen on the CT brain scan

2.3.4 Transcranial Doppler ultrasound results

2.3.5 Isotope Mean Cerebral Transit Time results

2.3.6 Comparison of the Mean Cerebral Transit Time with the Transcranial Doppler results

2.3.1 Study population

From 25th November 1990 to 31st May 1991 170 patients were admitted to the Western General Hospital with a stroke documented in the North Lothian Stroke Survey. Ninety of these patients (53%) were included in the imaging study. Between the end of the North Lothian Stroke Survey and the 31st August 1991 a further 51 patients were admitted to the Western General Hospital with a stroke identified by Dr R Lindley on a daily search of the hospital and through referrals to the acute stroke treatment trials. Thirty of these (59%) were included in the imaging study. Reasons for exclusion of patients are given in Table 2.3.1. Fifty patients were unsuitable for the study because they were disabled or dependant prior to stroke, admitted electively for investigation of previous stroke, or admitted directly to the neurosurgeons with primary intracerebral haemorrhage. Thirty-three were missed because of admission on a Friday, Saturday, holiday or CT scanner service day. Eleven patients were incorrectly diagnosed by the admitting medical staff - some as strokes which were other pathologies (five), and vice versa (six).

It was not possible to perform an MCTT study in a further 35 patients because: a) the attending physician thought that the patient was too ill to be moved to the imaging department (although the patient could be transport-

ed and imaged on their bed) 10/35; b) the time lapse between the TCD and MCTT studies would have been more than twelve hours by the time the MCTT study could be performed due to ethical and logistical problems (14/35); c) there was no isotope available (the daily allocation for the study - two doses - had already been used) 8/35; d) the patient was discharged rapidly (2/35); or e) the patient refused to have the MCTT study (1/35). None of these exclusion criteria would apply if the MCTT was an established diagnostic test, rather than an experimental technique, and could be justified on clinical grounds. The imaging survey included at least 70% of suitable patients, a not unreasonable figure given the practical constraints of the Neuroradiology Department hours of work.

The direct comparison between the TCD and MCTT techniques was restricted to the 85 patients who had both studies done. However the results of TCD in all 120 patients will also be discussed as it will be useful to compare the patterns of vascular pathology as shown by TCD with the OSCP clinical classification.

2.3.2 Study Patient Characteristics

The mean age of the study group was 70 years (SD: 13 years). The youngest patient was 20 and the oldest 91 years.

TCD was performed in 108 patients with acute cerebral infarction and twelve with primary intracerebral haemorrhage

(PICH). Of these patients MCTT was performed in 76 with acute ischaemic stroke and nine with PICH.

When classified according to the OCSF, there were 33/108 TACI, 43/108 PACI, 19/108 LACI, 13/108 POCI in the infarct group who had TCD : 21/76 TACI, 25/76 PACI, 16/76 LACI and 8/76 POCI of these also had an MCTT study. There were 37/120 (31/85) patients with a past history of stroke or TIA.

The prevalence of cardiac disease, hypertension, or carotid stenosis as risk factors for stroke in the patients who had both TCD and MCTT studies is shown in Table 2.3.2. Several patients had more than one risk factor, for example 23 patients had cardiac disease and hypertension. Smoking, family history and history of peripheral vascular disease were not included because the primary concern was with medical conditions which might technically impair the MCTT result. Cardiac disease and hypertension might impair cardiac output (diluting and prolonging the isotope bolus), and carotid stenosis might slow the arrival of the isotope on the ipsilateral side of the brain. Smoking, family history of stroke and peripheral vascular disease were unlikely to influence the MCTT directly.

Cardiac disease in some form was present in three quarters of the TACI, PACI and POCI patients, but only 40% of LACI and PICH patients. A history of hypertension was most common in the POCI, then LACI and PICH patients. Carot-

id stenosis was the least frequent abnormality and was commonest in the TACI patients (42% of the 27 patients examined), followed by the PACI patients (24% of the 36 patients examined). Six of the TACI and one of the PACI patients died, and six PACI and four LACI patients were discharged before the Duplex carotid ultrasound examination could be performed. Most of the PICH and POCI patients did not have carotid Duplex examination because it was considered unethical to move them to the Neuroradiology Department (or detain them in the Department at the time of the CT scan) just for research purposes.

Additional evidence of possible impaired cardiac function, the patients' drug history, was examined. Fifty-seven patients were on one or more drugs for cardiac disease or hypertension : 28 were taking one drug, 21 were taking two drugs, five were taking three drugs, and three were taking four drugs.

2.3.3 Imaging Studies - CT brain scan results including:

- a) the interobserver reliability of the CT infarct classification, and
- b) the accuracy of the OCSF clinical classification in predicting the site of infarction on CT

All 120 patients had a CT brain scan. The mean time to the CT scan from the stroke was 2.2 days, SD \pm 2 days (Table 2.3.3a). The patients who on initial clinical examination appeared suitable for entry into a stroke treatment trial, or where the attending medical staff requested a scan, tended to have their CT brain scan sooner than those in whom the CT scan was not requested for clinical reasons.

- a) the interobserver reliability of the CT infarct classification

The interobserver agreement (Kappa) for the site and extent of the recent infarct, amount of mass effect (swelling) in the infarct and haemorrhagic transformation are shown in Table 2.3.4. The Kappa statistics represent the degree of agreement over and above that expected by chance.^{306,307} A Kappa of zero represents the degree of agreement expected by chance alone, a value of one indicates perfect agreement. It has been suggested that a Kappa statistic of less than 0.2 represent poor agreement, 0.21-0.4 fair agreement, 0.41-0.6 moderate agreement, 0.61-0.8 good

agreement and 0.81 -1.0 excellent agreement.³⁰⁷ The Kappa for infarct site and extent was 0.78 (95% Confidence Interval (CI) 0.69 to 0.87); for infarct swelling it was 0.8 (95% CI 0.68 to 0.92); and for infarct haemorrhagic transformation it was 0.3 (95% CI 0 to 0.77). Thus agreement was "good" and "excellent" for infarct site and extent and for infarct swelling respectively, but only "fair" for haemorrhagic transformation. However the poorer agreement for haemorrhagic transformation was due to disagreement over minor degrees of petechial haemorrhage, not over the presence of focal haematomas. There were no important disagreements over infarct swelling or site and extent. The Kappa for infarct site and extent for the subgroup of patients with medium to large cortical and subcortical infarcts (72 patients) was 0.87 (95% CI 0.77 to 0.97), and was 0.59 (95% CI 0.42 to 0.76) for the subgroup of patients with small to medium sized cortical and small subcortical infarcts (46 patients). This indicated that the interobserver agreement for the site and extent of the infarct in patients with large infarcts was "excellent" as was the agreement for infarct swelling. The agreement for the site and extent of smaller infarcts was only "good" due to more disagreement about a) which "hole" in the brain was the recent infarct and b) when a large cortical sulcus was actually an infarct or just an enlarged space. Thus for the two experienced neuroradiologists at least, the CT infarct classification seemed simple

to apply and reliable with good to excellent interobserver agreement.

b) the accuracy of the OCSF clinical classification in predicting the site of infarction as seen on CT

The CT brain scan findings for all 120 patients are shown in Table 2.3.5 and their OCSF clinical syndrome. Table 2.2.2 shows the OCSF clinical syndromes and CT infarct appearances considered to be compatible, but briefly a medium to large sized MCA territory cortical infarct or a large sub-cortical infarct (more than two cm diameter) was felt to be compatible with a TACI clinically. A small or medium sized MCA territory cortical infarct and possibly a large sub-cortical infarct were felt to be compatible with a PACI. Small deep subcortical infarcts (less than 1.5 cm diameter) were compatible with a LACI. Infarcts in the brain stem, cerebellum or occipital lobes were compatible with the clinical diagnosis of a POCI.

In the patients diagnosed clinically as a TACI (33) the CT brain scan showed a medium to large MCA territory infarct in 30 (91%). In three patients the CT brain scan showed that the clinical diagnosis of infarct site and extent was wrong - two patients had infarcts of the whole PCA territory (left side) considered to be inappropriate, and one patient had only a small cortical MCA territory infarct considered appropriate as the patients symptoms had

improved rapidly during the first 48 hours after symptom onset. This latter patient had presented with a right hemisphere TACI syndrome which rapidly improved to a PACI syndrome (weakness of the left hand only) within 48 hours of onset. The admission CT brain scan (performed within twelve hours) was normal in only one TACI patient, the rest all showing subtle but definite evidence of the full extent of their infarct on the admission CT scan (confirmed by at least one follow up CT brain scan).

In the patients diagnosed clinically as a PACI (43) the CT brain scan showed a small to medium sized MCA territory infarct in 27 (63%), and an infarct of the borderzone between the MCA and PCA territories (both right hemisphere) in two (5%). In seven patients the CT brain scan failed to show a recent infarct - "negative" scan - (16% - one patient had a negative follow up CT brain scan and six did not have a follow up scan). In seven patients (16%) the CT brain scan showed that the clinical diagnosis of the site and extent of infarction was wrong : one patient had an infarct of most of the right MCA territory (inappropriately large for a PACI), one had an infarct of part of the right PCA territory and five (12%) had lacunar infarcts (all five were in the left cerebral hemisphere) all considered inappropriate. The patient with the infarct of most of the MCA territory was elderly, there was some difficulty in assessing her, and debate about whether she should be classified as a TACI or

PACI. The incorrect diagnosis of the five lacunar infarcts (on CT) as PACI syndromes clinically may have occurred because of occasional problems in differentiating between minor degrees of dysphasia and dysarthria (particularly as all were in the left hemisphere) and whether or not a monoparesis was affecting the whole of or only part of a limb.

In the patients diagnosed clinically as LACI syndromes (19) the CT brain scan showed a small subcortical (lacunar) infarct in eleven (59%), and a small infarct in the white matter lateral to the lateral ventricle in the borderzone between the MCA and PCA (small centrum semiovale infarct) in one (5%). The CT brain scan was negative in five (26% - one patient had a negative follow up CT brain scan and four did not have a follow up scan). The CT brain scan showed the clinical diagnosis to be wrong in two patients (10%) who had small cortical MCA territory infarcts (one in each cerebral hemisphere) and should have been classified as PACI syndromes.

There were 13 patients diagnosed clinically as POCI syndromes of whom 8 (61%) had an infarct in the brain stem, cerebellum or occipital lobes on their CT brain scan. In five, CT failed to show a recent infarct (38% - one patient had a negative follow up CT brain scan and four did not have a follow up scan). No infarcts were found in the carotid territory in the POCI patients.

CT showed intraparenchymal haematomas in 12 patients,

considered probably to be primary in origin. The haematomas were of various sizes and in various sites.

The clinical diagnosis was compared with the CT brain scan diagnosis for overall agreement. The sensitivity, specificity, positive and negative predictive values (PPV and NPV respectively) and accuracy of the OCSF clinical classification for the site and extent of the infarct as shown on CT scanning are shown in Table 2.3.6. Considering the 91/108 patients whose CT brain scan showed a definite recent infarct, the OCSF classification was correct in 80 (88% 95% CI 77 to 92%). The accuracy, sensitivity, specificity, PPV and NPV were best for the TACI patients. For the analysis of all 108 patients, where in some PACI, LACI and POCI patients the CT brain scan failed to show a recent infarct, a "best" and "worst" scenario have been calculated. "Best" scenario would be if the patients with persistently negative CT scans did indeed have a recent infarct in the area of brain predicted clinically. "Worst" scenario would be if the patients with persistently negative CT scans actually had an infarct in part of the brain outside the area predicted clinically. The "best" scenario PPVs were 0.84, 0.89 and 1.0 for the PACI, LACI and POCI patients respectively, but dropped to 0.67 (PACI), 0.63 (LACI), and 0.61 (POCI) for the "worst" scenario. The true PPVs probably lie somewhere in between these values. Excluding the patients whose CT scan failed to show a recent infarct from

the analysis gives PPVs of 0.81, 0.86 and 1.0 for the PACI, LACI and POCI patients respectively. The true accuracy of the OCSF clinical classification probably lies somewhere in between the "best" and "worst" scenarios, and is not best represented by excluding those patients whose CT scan failed to show a recent infarct.

Therefore in this group of hospital-admitted stroke patients, the OCSF clinical classification of cerebral infarction was shown to be reasonably accurate in predicting the site and extent of cerebral infarction as seen on the CT brain scan. The most frequent clinical error was diagnosing a PACI clinically in patients whose CT scan showed a recent lacunar infarct. The cause of the diagnostic error seems to have been in distinguishing minor dysarthria from dysphasia. The other main error was in diagnosing an MCA syndrome clinically (two TACI and one PACI) in patients with a PCA territory infarct on CT scan. This confusion has been described previously and occurs because proximal PCA occlusion may cause infarction of the temporal lobe and lead to hemiparesis and speech disturbance in addition to visual field loss.³⁰⁸ The clinical errors which occurred were relatively minor, were mainly in patients with small infarcts and are probably avoidable with greater awareness of the potential sources of error.

A final caveat to the use of CT brain scanning as the standard against which to judge the clinical diagnosis was

that small infarcts (anywhere in the brain) were difficult to diagnose particularly if the patient had marked cerebral atrophy or periventricular low attenuation areas. It was useful to have a normal admission CT brain scan followed by a scan showing a new abnormality a few days later because that was the best way of being sure that the visible lesion was the cause of the symptoms. In patients whose admission CT scan already showed a small infarct, particularly if it was a lacune, it was more difficult to be certain that the visible lesion was definitely the cause of symptoms. This was reflected in the lower Kappa value for the group of patients with small cortical and subcortical infarcts (0.59) compared with the Kappa for the group of patients with large cortical and subcortical infarcts (0.8) on blind independent viewing of the CT brain scans by the same two neuroradiologists. Had the ten patients with PACI and LACI syndromes and negative admission CT brain scans without a follow up CT scan had a repeat scan some recent symptomatic lesions might have become visible. Of the four PACI and LACI patients with negative admission CT brain scans who did have a follow up scan, one of each became positive and one of each remained negative even up to twelve days after the stroke.

For the following comparison of the pattern and extent of cerebral arterial occlusion as shown by TCD and MCTT, the combined "surrogate gold standard" of clinical and CT findings was used (Table 2.3.7). Patients whose CT brain

scan failed to show a recent infarct were classified as "unconfirmed" PACI, LACI, or POCI. Patients with a borderzone infarct on the CT brain scan were classified as "borderzone" PACI or LACI. The final number of patients according to the "surrogate gold standard" who had TCD was 31 TACI, 30 PACI, seven unconfirmed PACI, two borderzone PACI, 16 LACI, five unconfirmed LACI, one borderzone LACI, 11 POCI, five unconfirmed POCI and 12 primary intracerebral haemorrhages. The number of patients who also had an MCTT study was 21 TACI, 23 PACI, three unconfirmed PACI, two borderzone PACI, 15 LACI, three unconfirmed LACI, one borderzone LACI, eight POCI and nine PICH.

2.3.6 Imaging Studies - Transcranial Doppler Ultrasound results

All 120 patients had a TCD study as soon as possible after symptom onset. In 14 patients (11%) it proved impossible to obtain a diagnostic signal through the temporal bones, though signals could be obtained through the orbits. This failure rate was similar to that found by previous investigators.^{128,133,140,141}

The mean end tidal CO₂ during the TCD studies was 4.4% (95% CI 3.2% to 5.6%).

The mean time from symptom onset to initial TCD study was 1.8 days (SD +/- 2.9 days). The mean time to first TCD study by stroke type is shown in Table 2.3.3b. The PACI

patients had a longer mean time to the first TCD study (2.4 days) because of the inclusion of three patients in the calculation who were not imaged until more than ten days after symptom onset. The mean time to TCD for the PACI group without these three was 1.5 days (SD +/- 1.8). In these three patients, the true time of symptom onset was not clear when first seen, but it was decided that these patients should be included because the comparison with the MCTT was still useful.

The cerebral blood velocity pattern shown by the first TCD after admission to hospital is shown in Table 2.3.8. In Table 2.3.8 the figures in bold refer to the 85 patients who had both a TCD and an MCTT study but the following text refers mainly to the 120 patients who had TCD for clarity. In 14/120 patients it proved impossible to obtain a Doppler signal through the temporal bone windows (12%, 95% CI 7% to 22%). In 11 of the 85 patients who had an MCTT study the Doppler signal was unobtainable through the temporal bone windows (13%, 95% CI 7% to 22%).

In the thirty-one patients with large MCA territory infarcts (surrogate gold standard : TACI) the symptomatic MCA blood velocity was normal in four (13%) and appropriately reduced (by more than 25% of the asymptomatic MCA blood velocity) in 26 (84%). TCD was unsuccessful in one patient.

In the 30 patients with a small to medium sized MCA territory infarct (surrogate gold standard : PACI) TCD was

normal in eleven (37%), appropriately reduced compared with the asymptomatic MCA in 14 (47%) and reduced by more than was considered appropriate in two (7%) ie virtually undetectable MCA signal. One of the two patients with a "borderzone" PACI infarct had a normal MCA blood velocity, and TCD was unsuccessful in the other. Five of the seven "unconfirmed" PACI patients (66%) had normal MCA blood velocities, one had an appropriately reduced MCA blood velocity and in one TCD was unsuccessful.

In the 16 patients with lacunar infarcts (surrogate gold standard : LACI) TCD was normal in eight (50%), showed an inappropriate reduction of the MCA velocity in four (25%), and was unsuccessful in four (25%). The one patient with a "borderzone" LACI infarct had an inappropriately reduced MCA blood velocity. Four of the five "unconfirmed" LACI patients had normal MCA blood velocities, and in one TCD was unsuccessful.

In the 16 patients with posterior circulation infarcts (surrogate gold standard : POCI) 15 (94%) had normal MCA blood velocities and TCD was unsuccessful in one. The PCA, BA and VA blood velocities will not be discussed.

Of the 12 patients with primary intracerebral haemorrhage, seven (58%) had normal MCA blood velocities, three (25%) had an inappropriately reduced MCA blood velocity, and TCD was unsuccessful in two.

Thus the TCD result was considered "appropriate" to

the surrogate gold standard in 92/120 patients, or 77%, 95% CI 69% to 84% (64/85, or 75%, 95% CI 65% to 84%), assuming that all TACI patients should have had some evidence of impaired flow in the symptomatic MCA. The proportion of patients with "inappropriate" TCD findings was 14/120 patients, or 12% (10/85, or 12%). If it is considered that the patients with a TACI were likely to have an MCA main stem or major branch occlusion, and the patients with PACI, LACI, POCI and PICH should have had a patent MCA main stem and major branches (though PACI patients could have had MCA branch occlusions) then the accuracy of TCD for detecting MCA main stem or major branch occlusions was 86% (95% CI 75% to 94%). The sensitivity, specificity, PPV and NPV for TCD detection of MCA main stem or branch occlusion is shown in Table 2.3.9. Conversely the ability of TCD to demonstrate likely MCA patency (ie patients with a LACI syndrome) is shown, with the MCTT results in Table 2.3.13.

TACI infarcts should be due to MCA main stem or major branch occlusion and consequently be associated with the greatest decrease in the symptomatic MCA blood velocity. However a normal blood velocity might be found in the main stem of the MCA if early spontaneous reperfusion had occurred prior to the first TCD study, or the occlusion was in a major branch but the flow in the patent branches was increased in an effort to supply collateral channels. Four of the TACI patients had a normal MCA blood velocity in the

symptomatic MCA on the first study after admission to hospital. One of them first evaluated with TCD six hours after the stroke had had a myocardial infarct six days previously and was having paroxysmal atrial fibrillation. On the morning of the stroke she had had a negative transthoracic echocardiogram (immediately prior to the stroke), but cardioembolic stroke was considered most likely. Her CT brain scan showed an infarct of the posterior part of the peripheral MCA territory so she most likely had an embolic occlusion of a large MCA branch which could be compatible with a normal blood velocity in the MCA main stem whether the branch was blocked or not. Another TACI patient with normal symptomatic MCA blood velocity (twelve hours after the stroke) presented with the stroke but in retrospect had had a "silent" myocardial infarction immediately prior to the onset of the stroke (diagnosed on sequential cardiac enzyme and ECG changes). Her CT brain scan showed infarction of most of the MCA territory. She had a tight stenosis of the ipsilateral ICA origin, so it is possible that her stroke was due to hypotension at the time of the myocardial infarct leading to impaired perfusion due to carotid stenosis. One TACI patient with normal symptomatic MCA blood velocity (at 1.5 days after the stroke) had infarction of the anterior half of the peripheral MCA territory in keeping with occlusion of a large MCA branch which could be compatible with a normal blood velocity in the MCA main stem whether the

branch was still blocked or not. The fourth TACI patient with normal symptomatic MCA blood velocity did not have the TCD until two days after the stroke by which time spontaneous recanalisation might have occurred.

PACI strokes if large (ie two of the three components of a TACI syndrome) would be expected to be due to a large MCA branch occlusion so could be associated with some decrease in MCA velocity, but the small PACI strokes (ie only one of the three components of a TACI syndrome) due to small peripheral MCA branch occlusion would not. One of the two PACI patients with greater reduction in their MCA blood velocity than was considered appropriate (when examined at 24 hours after the stroke) developed a striatocapsular infarct. She had occlusion of the ipsilateral ICA and reversed flow direction in the ipsilateral ACA. The MCA blood velocity had markedly improved two days later. This suggests that the infarct was due to terminal ICA and MCA origin occlusion correctly detected by TCD as a low initial velocity in the symptomatic MCA, but due to good cortical collateral arteries and early recanalisation of the MCA, the area of the infarct remained small causing only a PACI clinical syndrome. There was no good explanation for the inappropriately low MCA blood velocity at 24 hours in the other PACI patient.

Lacunar infarcts due to occlusion of small lenticulostriate arteries should not be associated with any de-

crease in MCA blood velocity therefore the decrease observed in four patients was considered inappropriate as it suggested the presence of a large MCA branch occlusion. One of these patients, with their infarct in the centrum semiovale borderzone, had an ipsilateral ICA occlusion and increased (presumably collateral) flow in the ipsilateral PCA. The reduced MCA blood velocity could be due to the blood travelling via a long clooateral pathway from the opposite hemisphere or basilar artery to reach the MCA. In the other three patients with LACI syndromes, there were only very minor reductions in the symptomatic MCA blood velocities (which perhaps should have been ignored) with no obvious reason.

Posterior circulation strokes (presumably due to vertebrobasilar/PCA disease) should be associated with normal MCA blood velocities. All the patients in whom TCD was successful had normal MCA blood velocities, even those with infarcts of the entire PCA territory. The PCAs are more variable anatomically and more difficult to detect reliably with TCD.¹⁴³ The failure to detect a PCA is less reliably associated with disease than is failure to detect an MCA, therefore (and in view of the small number of patients with posterior circulation ischaemia) analysis of the PCA velocities has not been performed.

Primary intracerebral haemorrhage should not have been associated with any MCA blood velocity change unless

the haematoma was large and compressed or displaced the MCA on the symptomatic side.¹⁶³ Of the three patients with reduced symptomatic MCA blood velocities, two had large haematomas in the temporoparietal lobes but only a minor reduction in ipsilateral MCA blood velocity, and one had a small haematoma but more marked MCA velocity reduction. The latter patient also had a stenosis of the ipsilateral ICA and increased velocity in the ipsilateral ACA suggesting the presence of coincidental atherosclerotic MCA disease.

Additional confirmation of the accuracy of TCD was provided by post mortem examination in two patients, and by cerebral angiography in four. In each case the vascular pathology had been correctly shown by TCD.

2.3.5 Imaging Studies - Isotope Mean Cerebral Transit Time

85 out of the 120 patients had an MCTT study. It was not possible to perform an MCTT study on 35 of the 120 patients because : a) the attending physicians thought that the patient was too ill to be moved to the imaging department (although the patient could be transported and imaged on their hospital bed) - 10/35; b) there was no isotope available (the daily supply had already been used - the supply of isotope was limited to two doses daily if used in the morning or one dose if not used until the afternoon) - 8/35; c) the time lapse between the TCD and the MCTT studies would have been more than 24 hours by the time the MCTT

study could be performed due to ethical and logistical problems (14/35); d) the patient was discharged rapidly (2/35); or e) the patient refused to have the MCTT study (1/35). None of these exclusions would apply if the MCTT was an established diagnostic test rather than an experimental technique, and could be justified on clinical grounds.

The patients' mean end tidal CO₂ during the MCTT studies was 4.3% (95% CI 3.2% to 5.4%). The difference between the end tidal CO₂s during the TCD and the MCTT studies was not significant (mean value during TCD studies : 4.4%, 95% CI 3.2% to 5.5%).

The timing of the MCTT studies is shown in Table 2.3.3c. The mean time to performing the MCTT was 33.6 hours (+/- 20 hours), slightly longer than the mean time to TCD (26 +/- 17.5 hours), reflecting the greater mobility of TCD. The mean difference between the time to TCD and to the MCTT studies from stroke onset was -8.6 hours (95% CI of the difference -6 to -11 hours).

Three of the MCTT studies were unsuccessful due to technical faults in acquiring or in processing the data (gamma camera failure or computer fault). In a further six patients the MCTT was non-diagnostic because of a poor isotope bolus input curve (visible on the computer screen during the acquisition phase of the study) due either to faulty injection technique (too large a volume, too slow an injection, injection through too small a gauge of needle,

partial extravascular injection) or to impaired cardiac function leading to dilution of the bolus as it passed through the heart. Thus there were nine patients in whom the MCTT was totally uninterpretable (10.5%, 95% CI 5% to 19%). There were a further six patients whose MCTT was symmetrically prolonged through both hemispheres (beyond the upper limit of normal) but who did not have a particularly prolonged and flattened input curve. The interpretation of this finding was uncertain. One patient had tight bilateral cervical carotid stenoses on Duplex carotid ultrasound examination but the other five had evidence of cardiac disease and will be discussed in detail below. If these six were also included as "unsuccessful" MCTT studies then the total number of unsuccessful studies was 15/85 (18%, 95% CI 10% to 27%). The difference between the proportion of TCD and MCTT studies which were unsuccessful was not significant (observed difference -5, 95% CI of the difference -20 to 10).

Table 2.3.10 shows the results of the MCTT studies by stroke type as determined by the "surrogate gold standard" of CT brain scan and OCSF clinical findings. In the 21 patients whose combined clinical and CT brain scan findings showed a TACI stroke, the MCTT was abnormal in all 16 patients (76%) in whom it was successful showing delay in transit in half or more of the symptomatic cerebral hemisphere in 15 patients and more rapid transit in the sympto-

matic hemisphere in one. Note that this latter patient had presented with a TACI syndrome which resolved to a mild PACI syndrome over five days. There was evidence of reperfusion on serial TCD studies. The faster transit in the symptomatic hemisphere would be in keeping with reperfusion, but without knowing which side was symptomatic, it would be easy to misinterpret this as delay in transit in the opposite (asymptomatic) hemisphere. The MCTT was unsuccessful in five patients (24%) due to dilution of the isotope bolus secondary to impaired cardiac function in four and generally prolonged transit time in one (with apparently satisfactory input bolus). Figure 2.3.1 illustrates the CT brain scan, TCD and MCTT findings in a patient with a TACI syndrome.

In the 23 PACI patients ("surrogate gold standard" : PACI) the MCTT was normal in four (17%) and was appropriately abnormal (prolonged transit in less than half of the symptomatic cerebral hemisphere) in thirteen (56%). In two patients (8%) the MCTT showed delay in transit affecting the whole hemisphere and this was felt to be inappropriate as it suggested a larger deficit than was apparent clinically or on the CT brain scan. One of these latter two patients had an ipsilateral ICA occlusion. The other patient had a TACI syndrome clinically at presentation which resolved to leave a minor PACI deficit within 24 hours (only a small cortical infarct was visible on the CT brain scan). As with the TACI patient mentioned above, the transit was faster through the

symptomatic hemisphere, the MCA velocity was normal on TCD, and this combination of findings suggests early spontaneous reperfusion of an initially large area of ischaemic brain. Again, not knowing which side of the brain was symptomatic, blind review of the MCTT study suggested that the abnormality was in the asymptomatic hemisphere. In the three "unconfirmed" PACI patients (PACI clinically but negative CT brain scan) the MCTT was normal in one, showed an appropriate abnormality in one and prolongation of the transit time affecting the whole hemisphere (considered inappropriate) in the other. In two patients with a PACI syndrome clinically and a borderzone infarct on the CT brain scan ("borderzone PACI"), one had an appropriate transit abnormality and the other had bilaterally prolonged transit. Figure 2.3.2 illustrates the CT brain scan, TCD and MCTT results in a PACI patient.

In the 15 patients with a lacunar infarct, the MCTT was normal in five (33%), and showed minor insignificant transit time asymmetry in a further four (27%) and was inappropriately asymmetrical in three (20%). All three patients with "unconfirmed" lacunar infarction, had a normal MCTT study. The one patient with a lacunar syndrome clinically, a borderzone infarct on the CT brain scan (small centrum semiovale infarct) and reduced blood velocity in the symptomatic MCA showed minor insignificant transit abnormality only. Figure 2.3.3 illustrates the CT brain scan, TCD

and MCTT findings in a LACI patient.

In the eight posterior circulation infarction patients the MCTT was normal in three, showed appropriate minor transit abnormalities in the posterior parts of the cerebral hemispheres in four patients and showed unexplained abnormal transit in the anterior part of the symptomatic cerebral hemisphere in one patient. Figure 2.3.4 illustrates the CT brain scan, TCD and MCTT findings in a POCI patient.

In the nine patients with primary intracerebral haemorrhage, the MCTT was normal in five, showed a minor insignificant transit abnormality in one and a large hemispheric deficit in one patient (considered inappropriate).

Thus the MCTT showed an "appropriate" result in 62 of the 85 patients (73%, 95% CI 62 to 82%). The sensitivity, specificity, PPV and NPV for the MCTT in detecting probable MCA main stem occlusions (ie the patients likely to have reduced blood velocity in their symptomatic MCA and a TACI syndrome clinically) are shown in Table 2.3.12. The accuracy of the MCTT and TCD in detecting a patent MCA (ie patients likely to have a LACI syndrome) is shown in Table 2.3.13.

Closer examination of the patients with non-diagnostic MCTT studies showed a higher frequency of certain markers of impaired circulatory function than in patients with studies which were considered to be non-diagnostic (Table 2.3.11). Atrial fibrillation (with rapid or controlled ventricular rate) or untreated congestive cardiac failure

were particularly likely to yield a non-diagnostic MCTT study (odds ratios 4.3 and 5.5 respectively) whereas a history of myocardial infarction or hypertension were not (odds ratios 1.5 and 0.5 respectively). Angina was apparently associated with greater likelihood of a non-diagnostic MCTT study, but this was probably due to the coexistence of atrial fibrillation in all three patients who had angina. Previous stroke had no influence on the technical adequacy of the MCTT : of the 31 patients with a history of previous stroke, 27 had diagnostic and four (13%) had non-diagnostic MCTT studies, compared with the 54 patients with first ever stroke in whom 43 had diagnostic and 11 (20%) had non-diagnostic MCTT studies.

2.3.6 Comparison of the Mean Cerebral Transit Time with the TCD results : a) the ability of each to demonstrate likely MCA patency or occlusion,
b) the results of the few follow-up MCTT studies performed and comparison with serial TCD examinations, and
c) the comparison of the absolute values of the hemispheric transit time and MCA blood velocity.

a) the ability of the MCTT and TCD to demonstrate likely MCA patency or occlusion

The accuracy and practicality of TCD and MCTT in

diagnosing the pattern and extent of cerebral arterial occlusion were compared in the 85 patients who had both studies using the combined CT brain scan and clinical findings as the "surrogate gold standard" for the likely site of cerebral arterial occlusion (Table 2.3.10).

TCD was unsuccessful due to poor temporal bone windows in eleven of the 85 patients (13%, 95% CI 7 to 22%). There were nine patients in whom the MCTT result was totally uninterpretable (10.5%, 95% CI 5 to 19%). There were a further six patients whose MCTT was bilaterally and symmetrically prolonged beyond the upper limit of normal who did not have a particularly prolonged or flattened isotope input curve. If these six were also included as unsuccessful MCTT studies then the total number of unsuccessful studies was 15 (18%, 95% CI 10.2 to 27.4%). The difference between the proportion of MCTT and TCD studies that were unsuccessful was not significant (observed difference -5, 95% CI -20 to 6).

The TCD result was considered "appropriate" in 64 of the 85 patients (75%, 95% CI 65% to 84%) and the MCTT showed an "appropriate" result in 62 of the 85 patients (73%, 95% CI 62 to 82%). If the patients who had a "bilaterally and symmetrically prolonged transit" were considered to have a "normal" result (ie no hemispheric asymmetry) then the proportion of patients with an "appropriate" MCTT result was 67 of the 85 (79%, 95% CI 67 to 87%). The proportion of

patients with "inappropriate" TCD findings was ten out of 85 or 12% (95% CI 6 to 21%), and the proportion with "inappropriate" MCTT results was nine out of 85 or 10.6% (95% CI 4 to 18%).

The patients in whom there was disagreement between the TCD and MCTT results were as follows. Four of the patients with clinical and CT brain scan findings compatible with a TACI, in whom the blood velocity in the symptomatic MCA should have been reduced compared with the asymptomatic side, actually had normal blood velocity in the symptomatic MCA on TCD. In two of these patients, the MCTT was technically a failure; in another the MCTT was non-diagnostic probably due to impaired cardiac function (the patient had recently had a myocardial infarct and was in atrial fibrillation); in the fourth, the MCTT showed a transit abnormality in the symptomatic cerebral hemisphere, but smaller than that expected from the CT and clinical features. This latter patient had ipsilateral ICA origin and MCA stenoses (diagnosed by Duplex examination of the cervical carotid arteries and TCD) and in retrospect had probably suffered a myocardial infarct immediately prior to the onset of the stroke symptoms. It is possible that the cerebral infarct was secondary to a hypotensive episode around the time of the myocardial infarct superimposed on the ICA and MCA stenoses, but that no actual mechanical arterial occlusion occurred. This would explain both the apparently normal MCA blood

velocity and the small transit abnormality on the MCTT, but is conjectural.

The patients with combined CT brain scan and clinical features in keeping with a PACI tended to have fewer abnormalities detected by TCD (10 normal : 11 appropriate) than by the MCTT (4 normal : 15 appropriate). This suggested that the MCTT was more sensitive to MCA branch occlusions than was TCD.

The patients with the combined CT brain scan and clinical features in keeping with lacunar infarction should all have had normal TCD and MCTT studies, but four patients had reduced blood velocity in the symptomatic MCA on TCD and three had prolonged transit in the symptomatic hemisphere on MCTT. Of the three patients with reduced MCA blood velocity, one had mildly prolonged transit in the symptomatic hemisphere; two had normal transit, and in the fourth an MCTT study was not performed. Of the remaining two patients with inappropriately prolonged transit time in the symptomatic hemisphere, one had normal symptomatic MCA blood velocity and TCD was unsuccessful in the other. There were no good explanations for the reduced MCA blood velocities, or the transit abnormalities in any of these patients. The patient with the borderzone LACI had decreased blood velocity in the symptomatic MCA probably due to ipsilateral ICA occlusion, as discussed above. The MCTT was normal.

The patients with posterior circulation infarction

all had normal MCA blood velocities as expected. The PCAs are difficult to evaluate with TCD as there is so much normal variation in the arterial anatomy therefore the PCA velocity findings are not regarded as reliable in acute ischaemic stroke. The MCTT showed transit abnormalities in the posterior part of the symptomatic hemisphere in four of the eight patients and was therefore considered quite sensitive to posterior circulation ischaemia.

If it is considered that the patients with a TACI clinical syndrome and an extensive MCA territory infarct on their CT brain scan should have had an MCA main stem or major branch occlusion and the patients with PACI, LACI, POCI and PICH should have had a patent MCA main stem and major branches (though PACI patients would have had minor MCA branch occlusions) then the sensitivity of TCD for detecting MCA main stem or major branch occlusion was 90% (95% CI 70 to 99%) and of the MCTT was 94% (95% CI 71 to 99%), if those patients with bilaterally prolonged transit were counted as "normal" MCTT results (Table 2.3.9 and 2.3.12). Using the same criteria, the specificity of TCD for MCA main stem or major branch occlusion was 85% (95% CI 72 to 93%), and of MCTT was 86% (95% CI 75 to 94%). The post test positive predictive value of TCD was 70% (95% CI 50 to 86%) and of the MCTT was 67% (95% CI 45 to 84%). The post test negative predictive value of TCD was 96% (95% CI 85.5 to 95.5%) and of MCTT was 98% (95% CI 90 to 100%). There was

no significant difference in any of these figures between the two techniques.

If it is considered that patients with lacunar infarction on the CT scan and a lacunar syndrome clinically should have had a patent ipsilateral MCA then the accuracy of TCD for detecting a patent MCA in patients with a LACI was 60% (95% CI 47% to 71%) and of the MCTT was 90% (95% CI 80% to 96%). The sensitivity, specificity, PPV and NPV as well as accuracy are shown in Table 2.3.13.

b) results of the few follow-up MCTT examinations performed and comparison with results of serial TCD examinations

The majority of the comparison described in Part Two was to determine the ability of TCD and the MCTT to diagnose the pattern of arterial occlusion on the first examination after symptom onset. However some patients with TACI or extensive PACI syndromes had serial TCD examinations as part of the study described in Part Three. Ten of these patients had a second MCTT study also. There were six patients with definite evidence of improved blood velocity in the symptomatic MCA on serial TCD examinations within the first two weeks of stroke onset. In all six the MCTT showed a less pronounced transit abnormality on the second study at seven to ten days compared with the admission MCTT study, which would be in keeping with improved blood flow to the symptomatic hemisphere. The other four patients, with no evidence

of any improvement in symptomatic MCA blood velocity on TCD within two weeks of stroke onset, showed no change in transit time through the symptomatic hemisphere on the second MCTT study, in keeping with persistent arterial occlusion.

Note that there were two further patients, one with a TACI and one a PACI clinical syndrome, whose symptoms resolved rapidly after admission. The TACI patient had reduced blood velocity in the symptomatic MCA on admission which increased to normal within the first three days of admission. The PACI patient had normal blood velocity from admission onwards. Both showed faster transit through the symptomatic hemisphere than through the asymptomatic on the MCTT study done at 36 hours after the stroke, but without the clinical information of which side of the brain was symptomatic, it would be easy to misinterpret this finding as delayed transit in the hemisphere which was actually asymptomatic.

There is therefore some evidence that the MCTT technique may show changes compatible with reperfusion, and further evidence of its agreement with the patterns of arterial occlusion as shown by TCD. It must be emphasised however that the ability of the MCTT to demonstrate reperfusion is based on a very limited patient sample and that the study was not primarily designed to examine serial MCTT findings. A much larger prospective study will be required to define the true accuracy of the MCTT in demonstrating

reperfusion.

c) the comparison of the absolute values of transit time and blood velocity

For a final comparison of TCD and the MCTT, the peak and mean blood velocities in the symptomatic and asymptomatic MCAs were plotted against the absolute values of the mean transit time from the part of the cerebral hemisphere corresponding with the MCA territory. When originally devised, the computer analysis of the MCTT image gave a numerical value for transit through the whole hemisphere (in seconds) and also subdivided each hemisphere into four rectangular parts giving a numerical value for transit through each quarter of the hemisphere (as in Figure 2.2.2). The division of the hemisphere into "boxes" seemed unphysiological and might not have allowed the best use to be made of the information yielded by the MCTT. The computer program was rewritten, subdividing each hemisphere into four "wedge" or "pie-shaped" segments, more closely corresponding with the major arterial territories (Figure 2.2.2b). To decide which, "boxes" or "wedges" was most likely to mirror the arterial territories, the blood velocities in the MCAs, ACAs and PCAs were compared with the transit times in the central two, the anterior and the posterior boxes and wedges respectively.

There was a slightly better correlation between the MCA blood velocity (peak and mean) and the wedge-shaped

divisions of the corresponding hemisphere than with the rectangular divisions. MCA peak velocity and MCTT wedges: correlation 0.57, R^2 0.33, $P < 0.0000$; MCA peak velocity and MCTT rectangles : correlation 0.54, R^2 0.29, $P < 0.0000$. Therefore for future studies looking more closely at individual arterial territories, the wedges should be used. The difference between the two methods is not great, probably because the number of pixels in each rectangle or wedge is small. However on theoretical grounds and on the results of this comparison between arterial blood velocities and transit through the anatomical area of brain corresponding with the arterial territory, the wedges appear to fit better with the blood velocities. The part of the cerebral hemisphere taken to correspond with the MCA territory was the middle two wedges shown in Figure 2.2.2.

It had previously been shown that the blood velocity was inversely proportional to the transit time, in that the lower the velocity, the longer the transit time.²¹⁴ This was because measurement of hemispheric transit time and MCA blood velocity both provide an index of velocity flow in the cerebral circulation. Volume flow is proportional to the fourth power of the radius of the artery whereas velocity flow is proportional to the second power of the radius. The non-linear relationship of the MCTT and the MCA blood velocity observed previously²¹⁴ suggested that changes in MCA blood flow velocity reflected changes in the dynamic ratio

between cerebral blood flow and cerebral blood volume³⁰⁹ assuming that the MCA radius and length remained constant (see discussion Part Two Chapter Four). Therefore in this comparison the reciprocal of segmental mean transit time was plotted against MCA blood velocity to obtain a linear relationship.

In the symptomatic hemisphere, the reciprocal of the transit time was significantly linearly related to the MCA blood velocity (Figure 2.3.5). Both the peak velocity and the mean velocity were closely correlated with transit time (correlation coefficient 0.58, R squared 0.33, $P < 0.0000$ and correlation coefficient 0.53, R squared = 0.28, $P < 0.0000$ respectively).

In the asymptomatic hemisphere, there was a less definite relationship between peak or mean MCA blood velocity and transit time (Figure 2.3.6), mean : correlation coefficient 0.096, R squared = 0.009, $P = 0.43$, and peak : correlation 0.07, R squared = 0.005, $P = 0.54$).

There are several possible reasons for this apparent discrepancy. In the asymptomatic hemisphere, the normal autoregulatory responses should be active, whereas in the symptomatic hemisphere, the damaged arteries and arterioles may no longer have been able to maintain normal cerebral blood flow so the cerebral perfusion reserve decreased and the transit time became prolonged. No correction was made for the patient's age, and as cerebral blood velocity has

been shown to decline slightly with age ¹³³ whereas hemispheric transit time is unaffected by age (at least in the 102 "patient controls" whose age was not specified),²⁰⁵ this may have influenced the relationship between transit time and blood velocity in the asymptomatic hemisphere. Plotting the transit time in the asymptomatic hemisphere against the patients' age suggested that there might be a relationship between the two : correlation 0.32, R^2 0.1, $P = 0.01$. Plotting the reciprocal of the transit time in the asymptomatic hemisphere against age yields an even stronger correlation : correlation -0.39, R^2 0.14, $P = 0.002$. Furthermore it is possible that when the cerebral circulation is functioning normally there may be a range of blood velocities for any given transit time and vice versa. It may be that it is only when the cerebral circulation is stressed that the relationship between falling blood velocity and prolongation of the transit time becomes more obvious. No account was taken of the patient's end tidal CO_2 either, but as the end tidal CO_2 was the virtually identical at the time of TCD and MCTT in each patient and alteration in end tidal CO_2 has been shown to exert the same magnitude of effect on blood velocity as on transit time,²¹⁴ it would seem reasonable to ignore end tidal CO_2 in the comparison.

Summary of Chapter Three

1. A broad cross section of acute ischaemic stroke patients were studied using the OCSF clinical classification, CT brain scanning, TCD and the MCTT.
2. Good agreement was found between the OCSF clinical classification of acute stroke syndrome, and the site and extent of cerebral infarction on the CT brain scan.
3. The method of classifying cerebral infarcts as shown on CT brain scans, intended to separate the effect of swelling in, and haemorrhagic transformation of the infarct from the infarct site and extent has excellent interobserver agreement between experienced neuroradiologists.
4. Transcranial Doppler ultrasound was unsuccessful in 11% of all patients. TCD had an accuracy of 86% in diagnosing MCA main stem occlusion.
5. The MCTT was as accurate as TCD in demonstrating likely cerebral arterial pathology with a similar failure rate.
6. The MCTT was more often non-diagnostic in patients with cardiac disease particularly atrial fibrillation. Presumably this was because impaired cardiac output diluted the isotope bolus.
7. In six patients with probable MCA main stem occlusion on admission, a second MCTT study showed a reduction in the hemispheric transit abnormality suggestive of reperfusion, supported by TCD findings of increasing blood velocity in the symptomatic MCA.

8. There is a linear relationship between TCD blood velocity and the reciprocal of the transit time in the symptomatic hemisphere, but not on the asymptomatic side. Possible reasons for this are discussed.

Table 2.3.1 Reasons for exclusion of patients from the TCD/MCTT imaging survey

Reason	NLSS*	Post NLSS	Total
Christmas or other holiday period (emergency service only)	9	7	16
More than two day lapse from symptom onset (eg admitted on a Friday)	7	6	13
Admitted electively for investigation of a minor stroke (many days after event)	15	N/R+	15
Admission direct to the neurosurgeons with suspected PICH	15	N/R+	15
Previous disabling stroke or dementia	15	5	20
Not diagnosed as a stroke until five or more days after symptom onset	5	1	6
Final diagnosis not stroke (eg TIA, cerebral metastasis)	4	1	5
CT scanner service day or breakdown	3	1	4
Stroke occurred in hospital and referral delayed	1	0	1
Reason not known	6	0	6
Total patients admitted to hospital	170	51	221
Total excluded from the study	80	21	101
Total included in the TCD/MCTT study	90	30	120

* NLSS = North Lothian Stroke Survey

+ N/R =no longer relevant as these patients were no sought after the end of the NLSS

PICH = primary intracerebral haemorrhage

Table 2.3.2 The prevalence of cardiac disease, hypertension, and carotid stenosis as risk factors for stroke in the study population by stroke clinical syndrome

	TACI 33	PACI 43	LACI 19	POCI 13	PICH 12
Total patients					
A) Cardiac Disease:					
No cardiac disease	9	14	11	3	7
Atrial Fibrillation	10	11	2	0	0
Previous Myocardial Infarction	8	11	3	2	0
Angina	5	8	1	0	1
Congestive cardiac failure - controlled	7	4	0	0	0
- active	0	1	0	0	0
Cardiac valve disease	2	5	1	0	0
Total with at least one cardiac abnormality (and % of total)	24(73)	29(67)	8(42)	10(76)	5(41)
B) Hypertension (treated controlled, treated uncontrolled, or untreated) :-					
number of patients affected (and % of total)	11(33)	12(28)	8(42)	9(69)	5(42)
C) Carotid Disease in the neck (diagnosed by Duplex carotid Doppler ultrasound) - symptomatic side only referred to (POCI patients either side of the neck):-					
Normal carotids	8	13	4	4	4
< 50% ICA stenosis	6	13	8	2	1
> 50% ICA stenosis	3	5	0	0	1
ICA Occlusion	7	3	2	0	1
Not examined	9	9	3	6	5
% with > 50% ICA stenosis (of those examined)	42	24	13	0	28

Table 2.3.3 Mean time from stroke onset to imaging studies

	TACI	PACI	LACI	POCI	PICH	ALL PATIENTS
A) Mean time to CT brain scan						
Mean time (days)	2.3	2.6	2.8	1.7	1.6	2.2
+/- one SD	2.2	3.7	4.4	1.9	1.5	2.0
earliest (days)	0.06	0.16	0.13	0.18	0.13	0.06
latest (days)	8.0	6.0	7.0	6.0	6.0	8.0

B) Mean time to first TCD study

mean time (days)	1.6	2.4	1.1	1.9	0.9	1.1*
+/- one SD	1.8	4	0.9	2.5	0.5	0.73

C) Mean time to first MCTT study

mean time (days)	2.5	2.3	1.7	0.85	3.1	1.41*
+/- one SD	2	2	1	0.5	3.5	0.85

* mean of difference between the time to the first TCD study and the time to the MCTT study (on a paired t-test) was -0.345 days, 95% CI = -0.45 to -0.24 days (ie -8 hours 20 minutes, 95% CI -10 hours 50 minutes to -5 hours 45 minutes).

Table 2.3.4 Interobserver agreement for the two experienced neuroradiologists using the CT infarct classification shown in Table 2.2.1 and Figure 2.2.1

Parameter of Infarct Examined	Kappa	(95% confidence interval)
Infarct site and extent (all scans)	0.78	(0.69 to 0.87)
Infarct site and extent (medium and large cortical and subcortical infarcts)	0.87	(0.77 to 0.97)
Infarct site and extent (small cortical and subcortical infarcts)	0.59	(0.42 to 0.76)
Infarct swelling	0.8	(0.68 to 0.92)
Infarct haemorrhagic transformation	0.3	(0.0 to 0.77)

Table 2.3.5 The OCSF classification in the patients with cerebral infarcts and the appearance of the infarct on their CT brain scan.

"Borderzone" infarcts are included as "medium-sized cortical MCA" (2 patients) or "small subcortical" (1 patient) infarcts where appropriate. Large, medium and small cortical, and large and small subcortical infarcts are defined in the methods (Part 2.2.6).

CT Brain Scan Diagnosis of Infarct Site	Clinical Diagnosis of Infarct Site				Total
	TACI	PACI	LACI	POCI	
Large or medium cortical, or large subcortical MCA/ ACA territory infarct	30	1	0	0	31
Medium or small cortical, or large subcortical MCA/ ACA territory infarct	1	29	2	0	32
Small subcortical infarct in the carotid territory	0	5	12	0	17
Occipital, brainstem or cerebellar infarct	2	1	0	8	11
No recent infarct visible	0	7	5	5	17
Total	33	43	19	13	108

Table 2.3.6 The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and accuracy of the OCSF clinical classification compared with CT scanning.
 "Best" scenario assumes that patients whose CT brain scan failed to show a recent infarct did actually have their infarct in the site predicted clinically; "worst" scenario assumes that these patients actually had their infarct in a part of the brain other than that predicted clinically.

Clinical Diagnosis of Infarct Site	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
TACI	0.97	0.96	0.94	0.99	0.96
PACI: best scenario	0.95	0.90	0.84	0.97	0.91
worst scenario	0.94	0.82	0.67	0.97	0.80
LACI: best scenario	0.77	0.98	0.89	0.94	0.94
worst scenario	0.71	0.92	0.63	0.94	0.89
POCI: best scenario	0.81	1.00	1.00	0.97	0.97
worst scenario	0.73	0.95	0.61	0.97	0.93

Table 2.3.7 The "surrogate gold standard" for the likely diagnosis of the site of cerebral arterial occlusion - the combination of the clinical findings (using the OCSF classification) and the CT brain scan result.

Number of patients with each stroke type		
	Number having : TCD only	TCD + MCTT
TOTAL	120	85
TACI/large MCA infarct	31	21
PACI/small-medium MCA or ACA infarct	30	23
"unconfirmed" PACI	7	3
"borderzone" PACI	2	2
LACI/small subcortical infarct	16	15
"unconfirmed" LACI	5	3
"borderzone" LACI	1	1
POCI/PCA, cerebellar or brain stem infarct	11	8
"unconfirmed" POCI	5	0
PICH	12	9

Table 2.3.8 The site of likely cerebral arterial occlusion as diagnosed by TCD in comparison with the combined OCSF clinical and CT brain scan "surrogate gold standard". Numbers in brackets refer to patients with "bilateral prolonged transit time" (see text for interpretation). The patients with "borderzone" PACI (2 patients) and LACI (1 patient) are included as PACI and LACI respectively.

Stroke Type :	TACI	PACI	PACI (unconf)	LACI	LACI (unconf)	POCI	PICH	TOTAL
---------------	------	------	------------------	------	------------------	------	------	-------

TCD findings in 120 patients :

Total number	31	32	7	17	5	16	12	120
normal	4	12	5	8	4	15	7	55
appropriate	26	14	1	0	0	0	0	41
inappropriate	0	2	0	5	0	0	3	10
unsuccessful	1	4	1	4	1	1	2	14

TCD findings in the 85 patients who also had an MCTT study :

Total number	21	25	3	16	3	8	9	85
normal	2	10	2	8	2	7	5	36
appropriate	19	11	0	0	0	0	0	30
inappropriate	0	2	0	4	0	0	2	8
unsuccessful	0	2	1	4	1	1	2	11

Table 2.3.9 The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and accuracy of TCD in diagnosing likely MCA main stem or major branch occlusion in both the 120 patients and the 85 patients who also had an MCTT examination, in comparison with the "surrogate gold standard". The "bilaterally prolonged" MCTT studies are counted as "normal" in this calculation, as they suggested that there was no interhemispheric asymmetry, and therefore no proximal MCA occlusion.

Number of patients	85	120
accuracy	86%	87%
95% CI	75 to 94%	77 to 94%
sensitivity	90%	87%
95% CI	70 to 99%	69 to 96%
specificity	85%	87%
95% CI	72 to 93%	77 to 94%
positive predictive value	70%	72%
95% CI	50 to 86%	55 to 86%
negative predictive value	96%	94%
95% CI	86 to 99%	86 to 98%

Table 2.3.10 The site of likely cerebral arterial occlusion as diagnosed by the MCTT (and TCD) in comparison with the "surrogate gold standard" of clinical and CT brain scan findings in the 85 patients who had both studies.

Numbers in brackets refer to patients with "bilateral prolonged transit time" (see text for interpretation). The patients with "borderzone PACI (2 patients) and LACI (1 patient) are included as PACI and LACI respectively.

Stroke Type :	TACI	PACI	PACI (unconf)	LACI	LACI (unconf)	POCI	PICH	TOTAL
Total number	21	25	3	16	3	8	9	85
TCD :								
normal	2	10	2	8	2	7	5	36
appropriate	19	11	0	0	0	0	0	30
inappropriate	0	2	0	4	0	0	2	8
unsuccessful	0	2	1	4	1	1	2	11
MCTT :								
normal	0	4	1	10	3	3	5	21
appropriate	16	15	1	0	0	4	1	41
inappropriate	0	1	1	3	0	1	1	8
unsuccessful	5(1)	5(3)	0	3(2)	0	0	2	15(6)

Table 2.3.11 The frequency of circulatory abnormalities in the patients with "satisfactory" and "unsatisfactory" MCTT results.

	MCTT : "satisfactory"	"unsatisfactory"	ODDS RATIO	95% CI
circulatory abnormality :				
untreated congestive cardiac failure	4	3	5.5	1 to 29
atrial fibrillation	10	5	4.3	1 to 16
angina	6	3	3.5	1 to 17
cardiac valve disease	4	2	3	0.5 to 16
previous myocardial infarct	18	4	1.5	0.4 to 5
hypertension	27	3	0.5	0.1 to 2

two or more "circulatory" abnormalities	19	4	1.3	0.4 to 5
one "circulatory" abnormality	23	7	3	1 to 10
no "circulatory" abnormality	28	1	0.1	0.02 to 1

TOTAL	70	12 (+ 3 failed studies)		

Table 2.3.12 The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and accuracy of TCD and the MCTT in diagnosing likely MCA main stem or major branch occlusion in the 85 patients who had both examinations, in comparison with the "surrogate gold standard". The "bilaterally prolonged" MCTT studies are counted as "normal" in this calculation, as they suggested that there was no interhemispheric asymmetry, and therefore no proximal MCA occlusion.

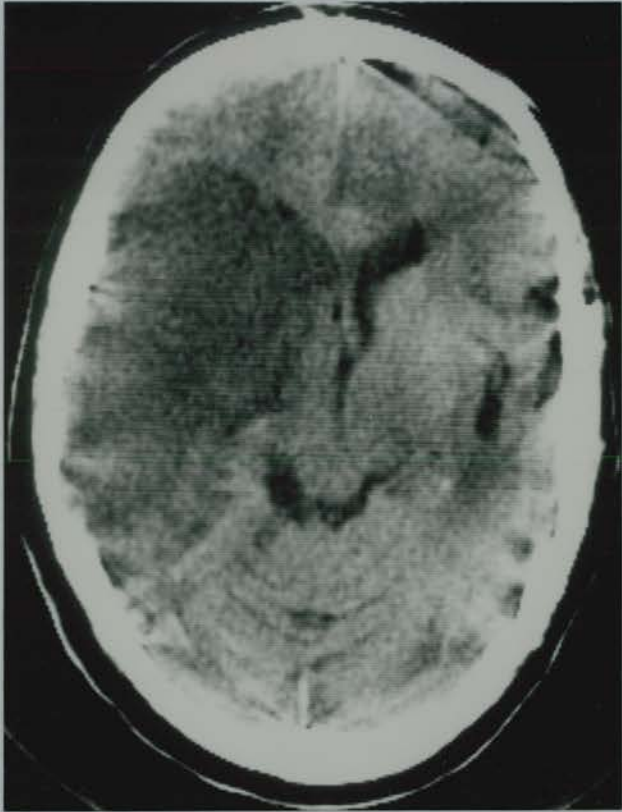
	TCD	MCTT
accuracy	86%	88%
95% CI	75 to 94%	77 to 99%
sensitivity	90%	94%
95% CI	70 to 99%	71 to 99%
specificity	85%	86%
95% CI	72 to 93%	75 to 94%
positive predictive value	70%	68%
95% CI	50 to 86%	45 to 84%
negative predictive value	96%	98%
95% CI	86 to 99%	90 to 100%

Table 2.3.13 Accuracy, sensitivity, specificity, positive and negative predictive values of TCD and the MCTT in predicting likely MCA patency in the 85 patients who had both studies, using the OCSF clinical/CT brain scan diagnosis as the "surrogate gold standard" for likely MCA patency. ie the ability of both techniques to identify patients likely to have a lacunar stroke.

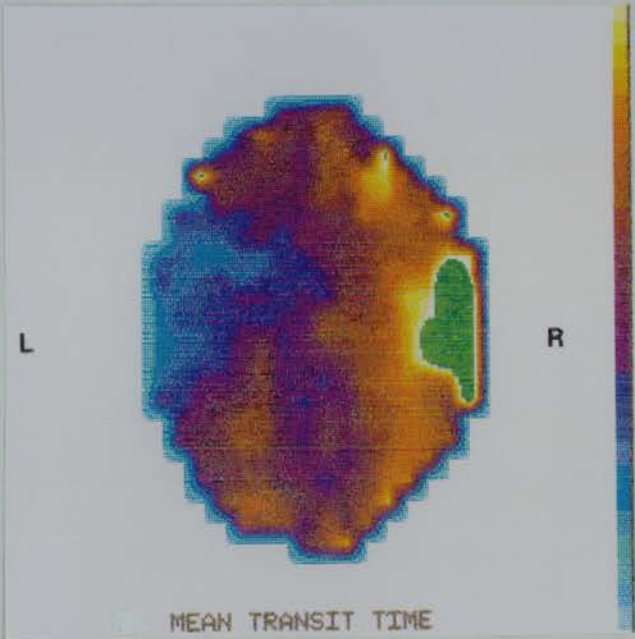
	TCD	MCTT
accuracy	60%	90%
95% CI	47 to 71%	80 to 96%
sensitivity	71%	81%
95% CI	42 to 92%	54 to 96%
specificity	56%	76%
95% CI	43 to 69%	62 to 87%
positive predictive value	28%	50%
95% CI	14 to 45%	30 to 70%
negative predictive value	89%	93%
95% CI	75 to 97%	81 to 99%

Figure 2.3.1 Patient with a Total Anterior Circulation Infarction : a) CT brain scan on day 3, b) MCTT study at 12 hours, and c) right PCA and left MCA blood velocities at 12 hours after symptom onset. No right MCA was detected. Note that the orientation of the MCTT is opposite to the CT scan.

a)



b)



c)

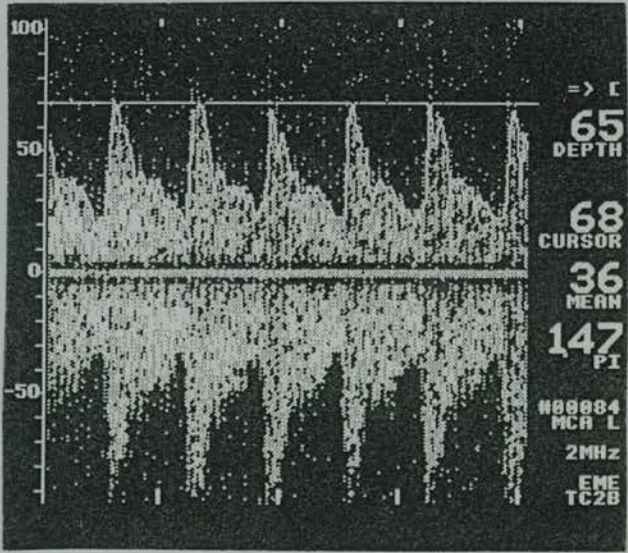
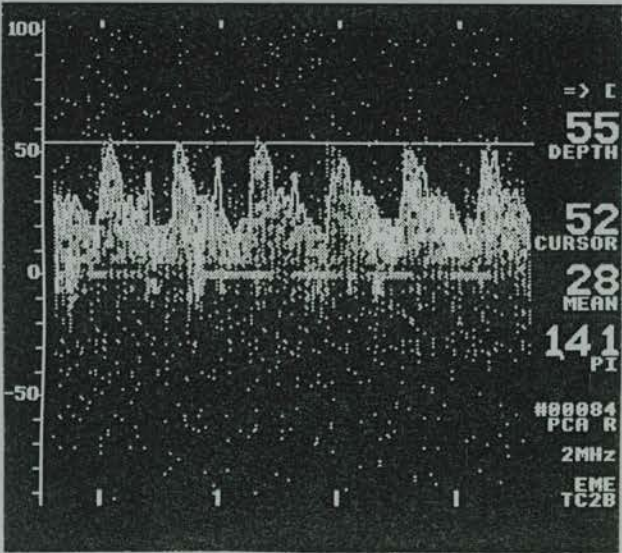
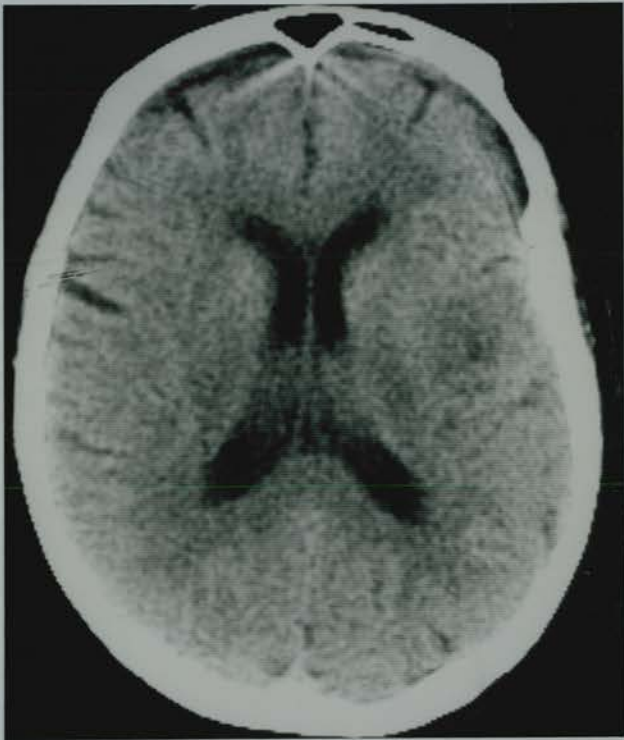
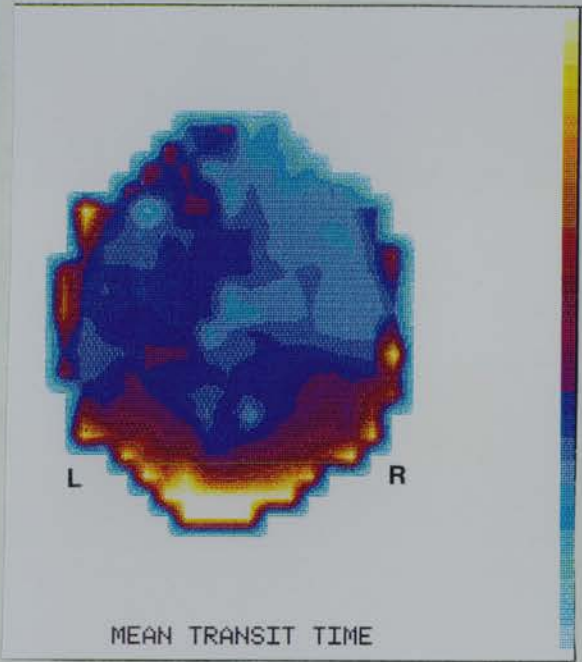


Figure 2.3.2 Patient with a Partial Anterior Circulation Infarction : a) CT brain scan at 4 hours, b) MCTT study at 4 hours, and c) right and left MCA blood velocities at 4 hours after symptom onset. Note that the orientation of the MCTT is opposite to the CT scan.

a)



b)



c)

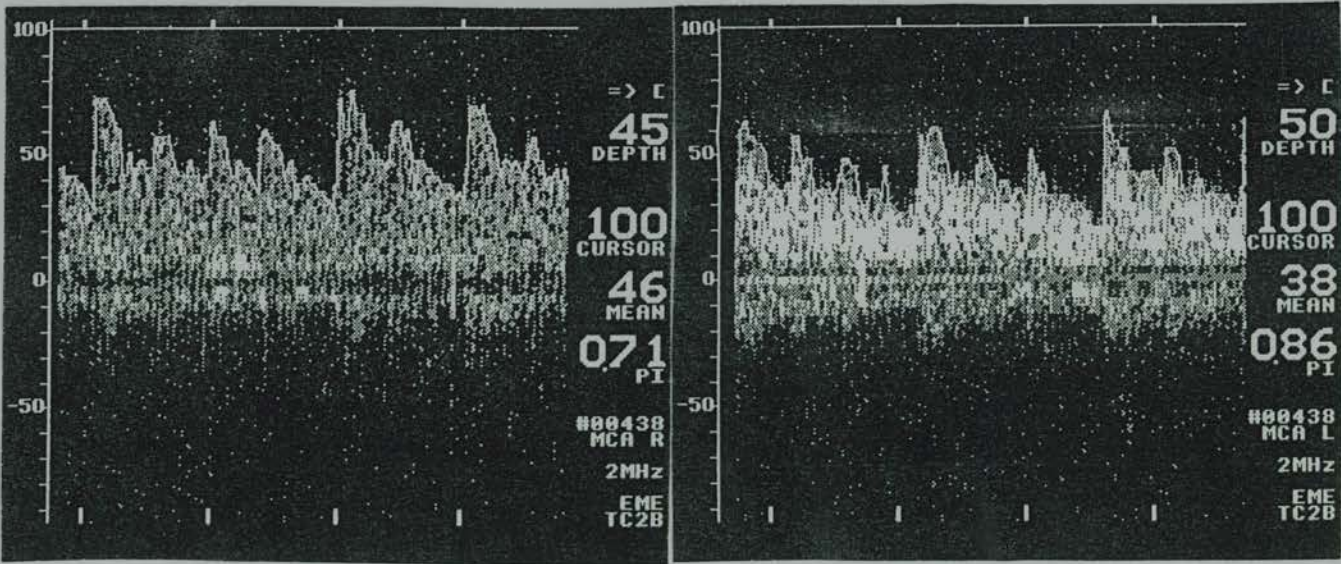
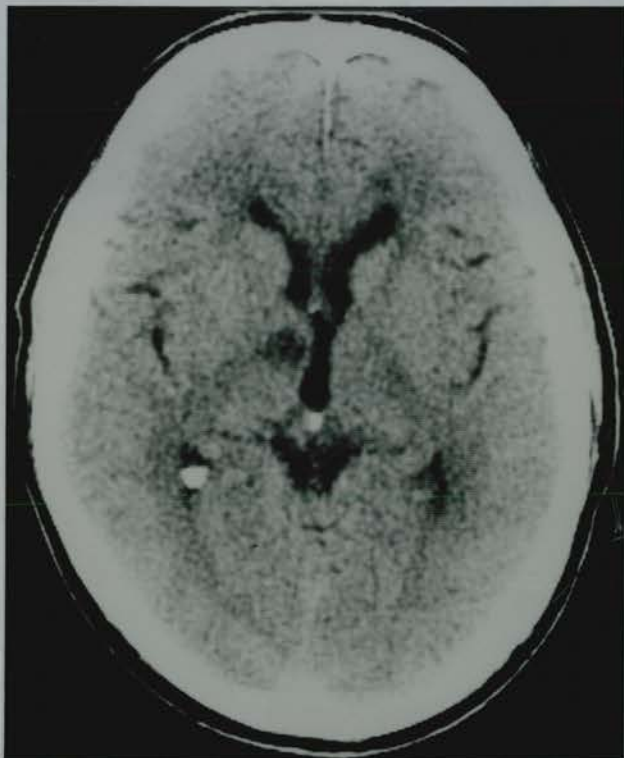
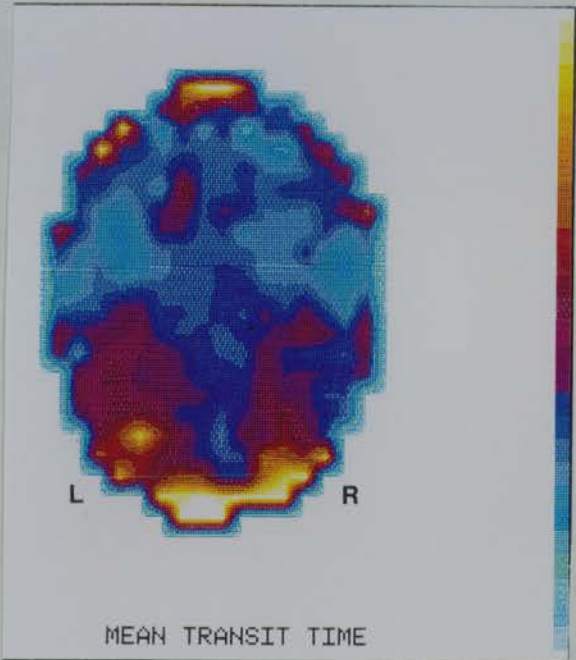


Figure 2.3.3 Patient with a Lacunar Infarction : a) CT brain scan at 24 hours, b) MCTT study at 6 hours, and c) right and left MCA blood velocities at 6 hours after symptom onset. Note that the orientation of the MCTT is opposite to the CT scan.

a)



b)



c)

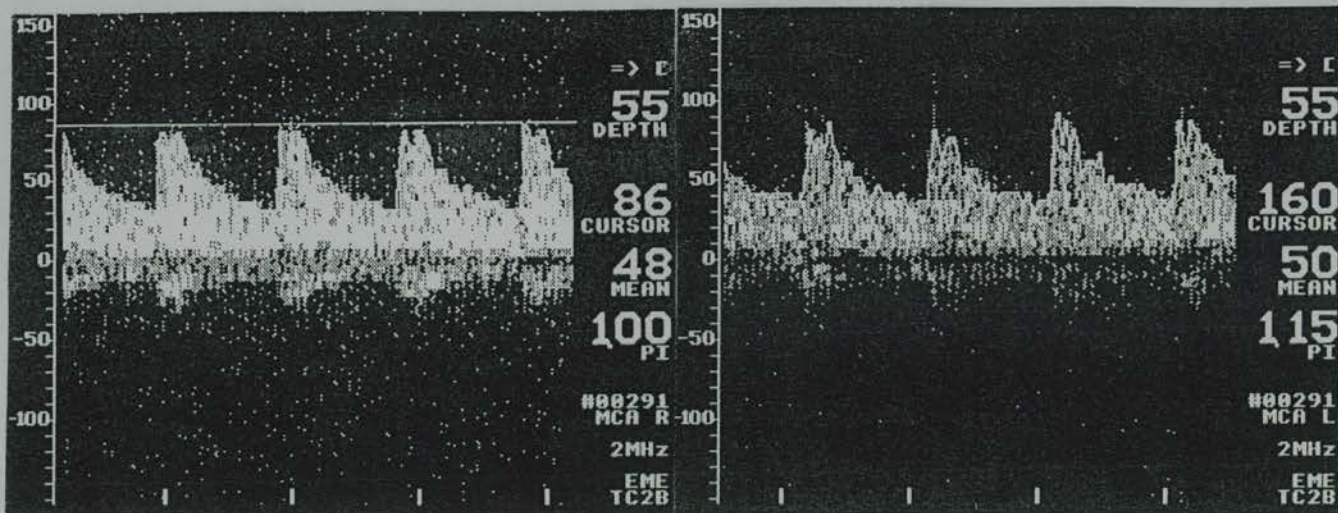
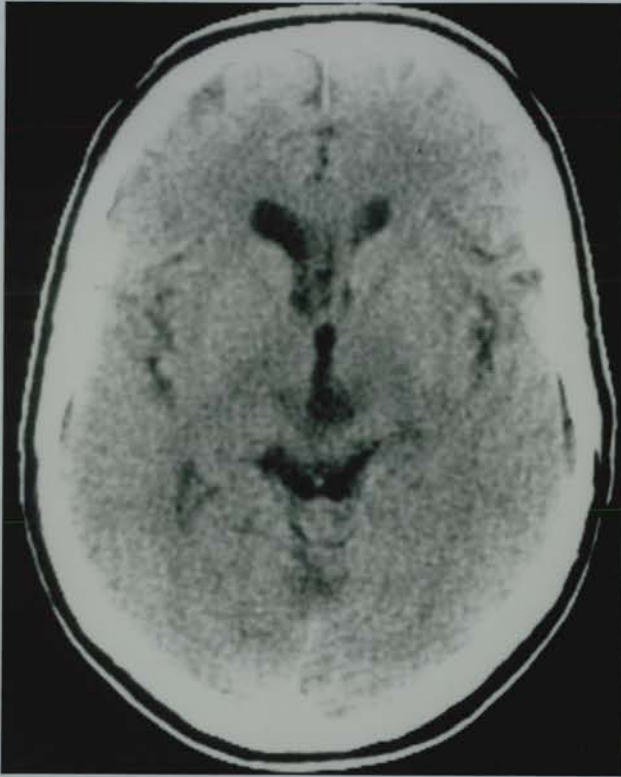
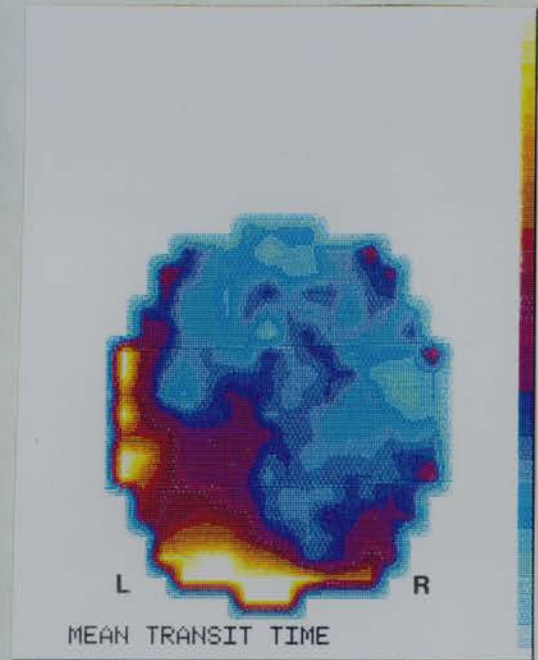


Figure 2.3.4 Patient with a Posterior Circulation Infarction : a) CT brain scan at 8 days, b) MCTT study at 7 hours, and c) right and left PCA blood velocities at 7 hours after symptom onset. Note that the orientation of the MCTT is opposite to the CT scan.

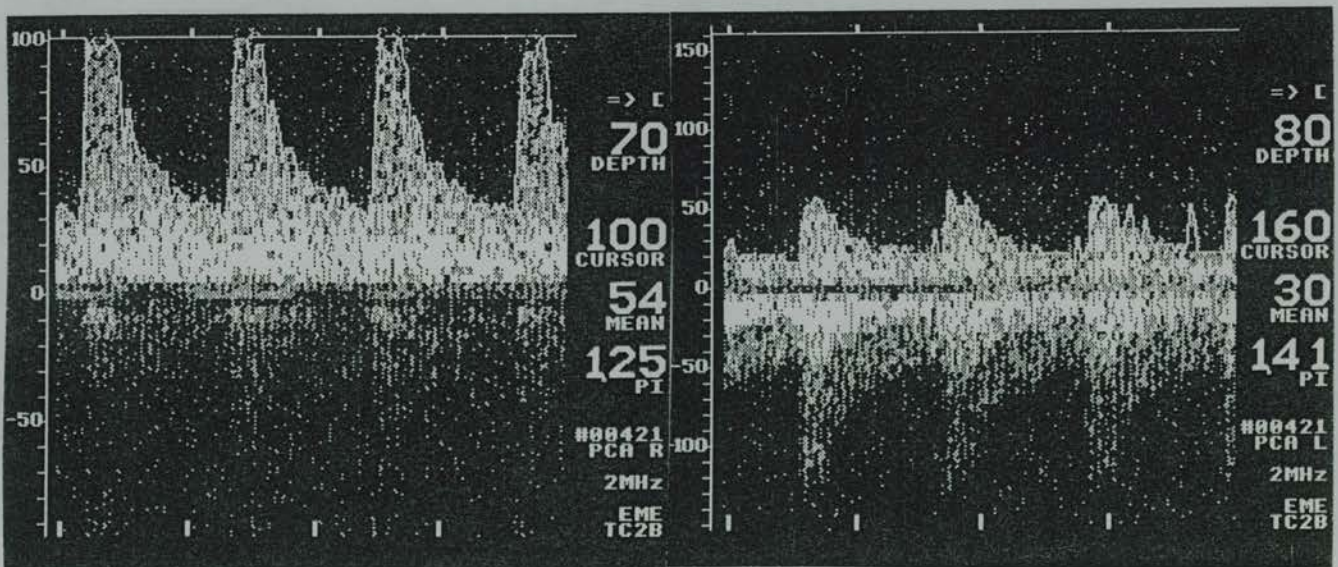
a)



b)



c)



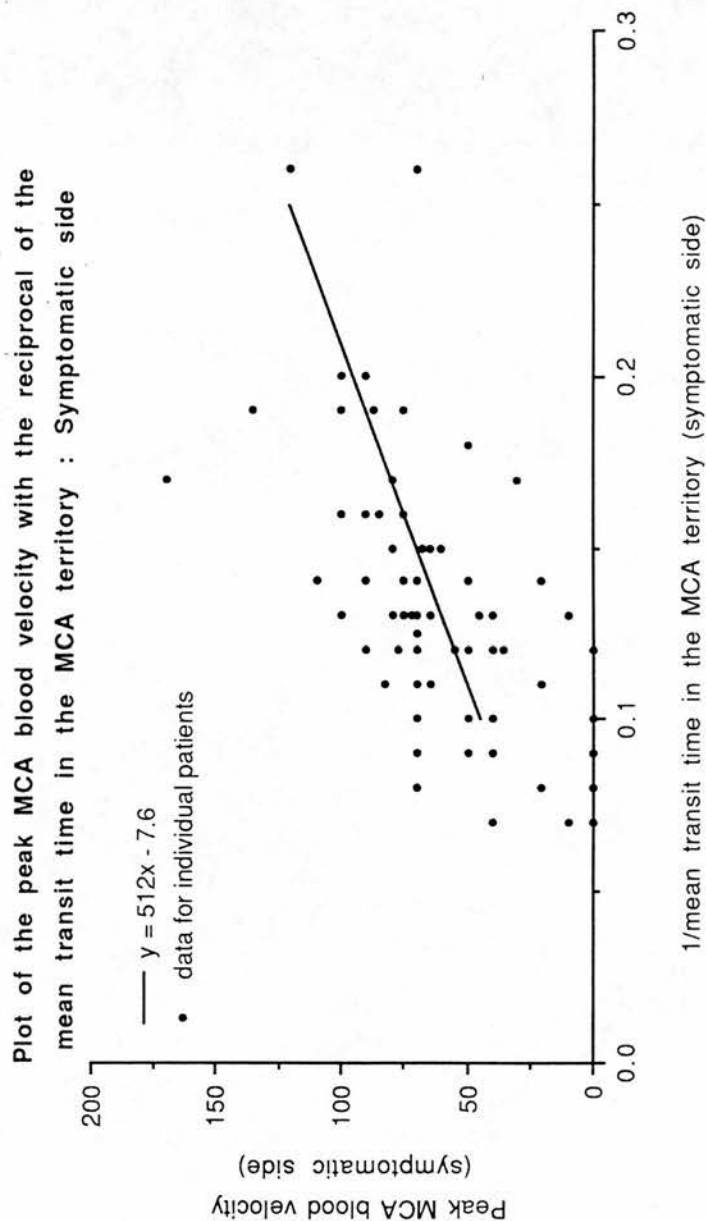


Figure 2.3.5 Comparison of the peak MCA blood velocity (in cm/sec) and the reciprocal of the Mean Cerebral Transit Time in the MCA territory - Symptomatic side. Correlation coefficient 0.58, R^2 0.28, $P < 0.000$. The absolute numerical value of the blood velocity and transit time have been used in this plot.

Plot of the peak blood velocity in the MCA with the reciprocal of the mean transit time in the MCA territory : Asymptomatic side

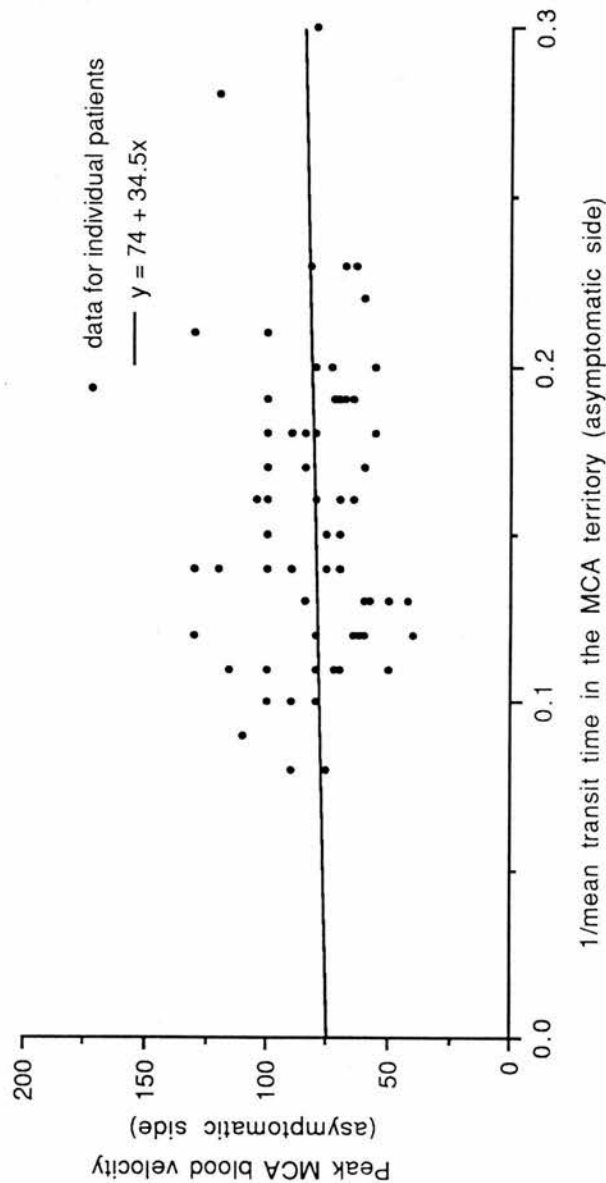


Figure 2.3.6 Comparison of the peak MCA blood velocity (in cm/sec) and the reciprocal of the Mean Cerebral Transit Time in the MCA territory - Asymptomatic side. Correlation coefficient 0.096, R^2 0.005, $P=0.54$. The absolute numerical value of the blood velocity and transit time have been used in this plot.

Part Two

Chapter Four

Evaluation of a Rapid Non-Invasive Method of Diagnosing Cerebral Arterial Occlusion : Comparison of Transcranial Doppler Ultrasound with the Isotope Mean Cerebral Transit Time in Diagnosing the Pattern and Extent of Cerebral Arterial Occlusion in Acute Ischaemic Stroke

Discussion

2.4.1 Study population

2.4.2 The accuracy of the OCSF clinical classification in comparison with CT brain scanning

2.4.3 The interobserver reliability of the CT infarct classification

2.4.4 The accuracy of Transcranial Doppler Ultrasound

2.4.5 The accuracy of the isotope Mean Cerebral Transit Time

2.4.6 On the comparison of the absolute values of middle cerebral artery blood velocity and hemispheric mean transit time

2.4.7 General points concerning the imaging investigation of patients with acute ischaemic stroke

Study population

The study population consisted of as many patients as possible admitted to our hospital with acute stroke. The largest group of patients excluded were those who reached hospital on a Friday afternoon, Saturday or Sunday so that the time lapse to the TCD and MCTT studies would have been longer than 48 hours from symptom onset. It is unlikely that patients who have their stroke towards the end of the week are very different from those who have their stroke early in the week, so it is not considered that this will have introduced any significant bias in terms of stroke type. Patients who were severely disabled prior to this stroke were excluded whether the disability was due to previous stroke or other cause and this may have introduced some bias. However patients with previous non-disabling stroke were included. Most of the other patients were excluded because they did not have an acute ischaemic stroke as the cause of symptoms. It was very fortunate that the North Lothian Stroke Survey was undertaken during the same period as the imaging studies as it gave an exact count of the number of patients admitted to our hospital with a stroke. Otherwise it would have been difficult to obtain reliable numbers easily. Hospital in-patient discharge statistics are unreliable with both significant false positive and negative diagnoses (Dr M S Dennis, personal communication).

The mean age of the study patients was 70 years which

is virtually the same as the mean age of the patients in the Oxfordshire Community Stroke Project.^{16,300} One third of the study patients had had a stroke previously and approximately two thirds had evidence of cardiac disease of some sort or hypertension. Therefore the study population is considered to be reasonably representative of hospital admitted ischaemic stroke patients. Patients with subarachnoid haemorrhage and primary intracerebral haemorrhage were largely excluded as not relevant to the study.

2.4.2 The accuracy of the OCSF clinical classification in comparison with CT brain scanning

At the time of the study, the OCSF clinical classification had not previously been evaluated prospectively. When originally devised, each patient in the OCSF was reviewed and their clinical and CT brain scan (where available) findings discussed before the stroke syndrome was diagnosed. That process is rather different to that which normally takes place in clinical practice where, especially for acute medical emergencies, it is necessary to decide on a working diagnosis prior to implementing sensible investigations and treatments. Therefore prospective assessment of the accuracy of a clinical classification is necessary before its true reliability can be established. The interobserver reliability of the OCSF clinical classification of acute stroke has been evaluated prospectively (blind to all CT brain scan or

other imaging results) by Dr M S Dennis and Dr R I Lindley and found to be "moderate" to "good".³¹⁰ The classification is practical enough for routine use to classify stroke patients in general hospital practice. The observers agreed in the majority of patients and the level of agreement is likely to represent the sort of agreement found in routine clinical practice. The level of agreement was similar to that found in a study by Shinar et al³¹¹ on interobserver agreement between staff neurologists with a special interest in stroke eliciting neurological signs in seventeen patients with stroke.

In the present study of hospital-admitted stroke patients, the OCSF classification was shown to be accurate in predicting the site and extent of cerebral infarction as shown on the CT brain scan. In the "worst" scenario, where the patients with negative CT scans might have had an infarct in a place other than that predicted clinically, the positive predictive value fell from around 0.8 (or "best" scenario) to around 0.7, with a similar effect on the sensitivity. However, this interpretation is unlikely to be completely correct and it is more likely that the true positive predictive value lies somewhere in between the "best" and "worst" scenarios. Excluding the patients whose CT scans did not show a recent infarct from the analysis would not give a better estimate of accuracy as there will always be some acute stroke patients with negative CT, or

even MRI, brain scans for whatever reason : the lesion might be too small to resolve with modern imaging, or there might have been early reperfusion in some way masking the lesion. Whatever the reason for negative imaging, these patients might represent a different subgroup of stroke patients, but it would be wrong to exclude them from analysis. Therefore, the accuracy of the OCSF clinical classification has been expressed as a range of possible values. MRI, with its greater sensitivity for small ischaemic lesions,^{281,283,285} might give a better estimate of the accuracy of the clinical classification. However MRI is less widely available than CT scanning (in the UK at any rate). It is a less practical technique for acutely ill, confused patients who may require sedation and the scanning times are longer than for CT. It may be difficult to exclude intracerebral haemorrhage very early after symptom onset with MRI,²⁸² so for all these reasons, MRI is unlikely to become a routine test for acute stroke, though it will be very useful in research.^{290,312}

The most frequent clinical error in this series was diagnosing a PACI clinically in patients who actually had a lacunar infarct on the CT brain scan (five patients). In all of these patients the infarct was in the left cerebral hemisphere and the source of difficulty seems to have been in distinguishing between dysarthria and minor degrees of dysphasia. This difficulty was also found in the Stroke Data Bank study of interobserver agreement for neurological signs

recorded for patients with acute stroke, where their Kappa value for language was 0.54 and for dysarthria was 0.53, both indicating "moderate" agreement only.³¹¹ Dysphasia plus hemiparesis implies a cortical localisation and is a PACI whereas dysarthria plus hemiparesis implies a subcortical localisation and is a LACI.²⁵ Of the two patients thought clinically to have a LACI (but with a small cortical infarct on their CT brain scan) one had a left and the other a right hemisphere infarct. In the patient with the infarct in the left hemisphere it was difficult to decide whether there was minor dysphagia or dysarthria. The other main source of error was in diagnosing an MCA syndrome clinically in patients with a PCA territory infarct on the CT scan (two TACI and one PACI patients). This confusion has been described previously and arises because proximal PCA occlusion may cause infarction of the temporal lobe and lead to hemiparesis and speech disturbance in addition to visual field loss.³⁰⁸

No clinical test, or radiological test for that matter) is 100% accurate and the OCSP clinical classification was intended to be a simple, rapid, fairly reliable and thus practical method of categorising acute ischaemic stroke patients, which would be clinically useful to predict prognosis, plan secondary prevention and aid communication and management decisions at a very early stage before any infarct is visible on the CT scan or indeed before CT can

practicably be performed. At present the main advantages are the prediction of outcome and improved interdisciplinary communication. For example 95% of patients with a TACI are dead or disabled at one year, compared with 45% of PACI, 33% of POCI and 33% of LACI (Figure 1.1.2).²⁵ PACI patients are more likely to have early recurrent strokes than LACI patients so should be investigated quickly to identify risk factors (for example carotid stenosis) for appropriate secondary prevention. As far as communication is concerned, describing a stroke patient as having had a "TACI" is much more informative than simply saying that the patient has a dense hemiparesis. "TACI" indicates that the patient is probably drowsy, may be dysphasic or have neglect (so be difficult to communicate with and manage), compared with a patient who has a dense hemiparesis due to a LACI who would have good comprehension, be alert and therefore easier to manage. By predicting the site and extent of cerebral infarction the clinical classification perhaps also predicts the underlying pattern of arterial pathology.³¹³ The clinical classification is also being used for risk/benefit analysis of clinical stroke subgroups in acute stroke treatment trials.³¹⁴ It is possible that, in the future, the classification could be used to identify quickly subgroups of acute ischaemic stroke patients with a particularly poor prognosis who might benefit from certain, perhaps more risky types of treatment should any of them be shown to work. The

OCSF classification may also remind doctors to examine stroke patients for specific abnormalities, such as parietal dysfunction and visual field loss, points which are easily and often overlooked by the inexperienced and lead to errors in diagnosing the site of the lesion, identifying risk factors, recognising the extent of the patient's disability, and initiating effective clinical management.

This prospective study has shown that usually the OCSF clinical classification does predict the site and extent of cerebral infarction. The clinical errors identified are considered to be relatively minor and probably avoidable with greater awareness of the pitfalls. The overall accuracy is excellent. It is important that clinical classifications of acute stroke are simple and quick to apply, so that doctors will be more likely to use them, the more likely that patients will be investigated quickly and appropriately to guide secondary prevention, and the more likely that acute stroke treatment trials will succeed.

2.4.3 The interobserver reliability of the CT infarct classification

The classification of cerebral infarcts as seen on CT brain scans was devised after a thorough review of the literature failed to reveal a method of describing cerebral infarct morphology which was sufficiently simple to use, and made any attempt to separate the effect of different varia-

bles on infarct appearance, in particular infarct swelling and haemorrhagic transformation.^{264,305} Templates for the very accurate identification of cerebral arterial territories have been described but these are necessarily complex and only refer to infarct site, not the other features.^{238,245} With increasing interest in treatments for acute ischaemic stroke and continued confusion over the relationship between reperfusion of the occluded artery, infarct swelling and haemorrhagic transformation, it will be important to be able to study cerebral infarct morphology closely. CT scanning is a very good way of doing this in life (MRI is also useful) as post mortem studies are hampered by the fact that the patient may not die until days or months after the stroke onset by which time the acute features of the infarct will have resolved. Also post mortem rates for patients thought to have had a stroke have declined in the USA and probably also in the UK, so there is less opportunity for pathologists to examine the brain after an acute ischaemic stroke.³¹⁵

The classification described was devised after review of many CT brain scans from acute stroke patients and was intended to reflect the frequently observed patterns of infarction. Although perhaps appearing complex at first, it proved remarkably simple to use. Only three codes were needed for describing haemorrhagic transformation and six for infarct swelling. More codes were required for infarct

site and extent but mainly because of the subdivisions of the MCA territory infarcts. As the majority of infarcts occur in the MCA territory and there was particular interest in factors which might influence infarct swelling, it was considered important to have sufficient MCA infarct subdivisions to allow definitive separation of the effect of infarct swelling from site and extent. If the classification were to be used for other purposes, then the MCA territory infarcts could be simplified to only four categories instead of eight.

The interobserver agreement for infarct site and extent (particularly for large infarcts) and infarct swelling between the two experienced neuroradiologists was excellent. It is therefore possible to use the classification as a means of separating the effect of infarct site and extent from infarct swelling. For example it is possible to distinguish reliably between an infarct of site and extent "60" with amount of swelling "2" and a "60" with amount of swelling "5".

The agreement for infarct haemorrhagic transformation was less good, but this was due to disagreement over the presence of minor amounts of petechial haemorrhage, not about focal haematomas. The margins of an infarct, particularly the cortical margins, may appear of higher density than surrounding normal brain. This may be partly an effect on the eye due to the low density of the infarct making the

adjacent normal cortex appear brighter, or there may be a genuine increase in tissue density around the margin of an infarct ascribed to luxury perfusion,^{258,262} or there may be true petechial haemorrhage.^{254,316} The disagreement over the presence of petechial haemorrhage may explain some of the large difference in haemorrhagic transformation rates reported in different CT (and MRI) studies. Some studies have reported rates of petechial haemorrhage up to 45%^{254,316} whereas others only found it in 5% of patients.²⁵⁵ There are other possible reasons for the wide variation in reported rates of haemorrhagic transformation between studies including bias in patient selection (all studies), concurrent treatment with antithrombotic drugs,^{254,269,316} differences between CT scanners,³¹⁷ and scanning at different times after the stroke,²⁷⁴ but poor interobserver agreement may have contributed. All studies of haemorrhagic transformation so far have been biased because only surviving patients were examined in the CT and MRI studies and only the patients who died were examined in the post mortem studies. Haemorrhagic transformation can occur without any symptomatic deterioration^{316,317} or could be the cause of sudden deterioration in the patient's clinical state leading to death. It is therefore not valid to exclude patients who were not scanned (or did not die) from the analysis. Nor is it reasonable to include only patients with "presumed cardioembolic stroke" or other subtype for example, as, with increasingly sophis-

ticated investigative tools, it is becoming clearer that it was probably not valid to make assumptions about the stroke aetiology as was done in previous studies. Only a study which includes all patients with ischaemic stroke who all have either serial CT (or MRI) examinations or post mortem can yield a true haemorrhagic transformation rate.

To reduce the interobserver disagreement, it would be possible to measure the brain tissue density directly from the image on the CT scanning console, but not so easily from the hard copy. However this would prolong the time taken to review and report the CT scans and would not be practical to do routinely, but greater awareness of this pitfall of interobserver reliability in reporting of petechial haemorrhage might help to improve accuracy.

Interobserver agreement was less good for the group of patients with small to medium sized cortical and subcortical infarcts. The mean age of the patients in the study was 70 years at which age generalised cerebral atrophy, periventricular white matter lucencies and enlarged perivascular spaces (in the internal capsule and basal ganglia) are common.³¹⁸ Patients with a history of previous stroke were also included in the study. Although a previous study found no evidence of bias in reporting lacunar infarcts on CT brain scans from accompanying clinical information²³² without any clinical information it can be difficult to discriminate small cortical infarcts from enlarged sulci and if

there are numerous "holes in the brain", to decide which is likely to be the cause of recent symptoms. The interobserver agreement for large cortical and subcortical infarcts was better as it was easier to identify and date large lesions. The infarct swelling codes were not intended to describe mass effect from large haematomas. The classification could equally be used to describe cerebral infarcts as seen on MRI. The interobserver agreement for the CT infarct classification was better than has been described previously for experienced clinicians using clinical stroke classifications.^{310,311,319} It was also on the whole better than the interobserver agreement reported in previous studies of CT scans in acute ischaemic stroke patients, which was in any case good.^{263,264}

Therefore the method of classifying cerebral infarcts as seen on CT brain scans is sufficiently good and reliable to be useful in stroke research as well as in clinical practice. Use of the infarct morphology classification would allow study of the effect of therapeutic interventions for acute ischaemic stroke, for example thrombolysis, neuroprotective agents, etc, on infarct morphology (swelling and haemorrhagic transformation) as surrogate, but useful, endpoints.

2.4.4 The accuracy of Transcranial Doppler Ultrasound

There have now been numerous studies of cerebral arterial blood velocities in acute ischaemic stroke,^{298,299,320} some with angiographic correlation,^{138,143,154,156,158,159} and some which matched the clinical stroke type (ie large artery occlusion or lacune) to the TCD findings.^{313,321} All have depended on identifying a reduced or "missing" arterial blood velocity signal in one of the basal intracranial arteries (usually the MCA) on the symptomatic side when compared with the asymptomatic side to diagnose arterial occlusion. Side to side variability in the peak and mean blood velocities in the basal intracranial arteries has been established in several studies, all of which were in agreement that a reduction in the mean blood velocity in the MCA of about 25% or more was abnormal.^{138,139,157} Therefore a reduction in arterial blood velocity greater than that is a reasonably reliable indicator of occlusion of the artery in one of the major branches or more proximally. In general, the greater the reduction in blood velocity on the symptomatic side relative to the asymptomatic, the more proximal the occlusion. Note however that it may be possible to record a near normal blood velocity from an MCA with a major branch occlusion if the blood flow in the patent branch has increased to supply collateral flow to the ischaemic brain supplied by the occluded branch, the net result being a "normal" blood velocity in the MCA

main stem. All of these factors must be taken into account when interpreting the TCD result, but in experienced hands TCD does appear to be a reliable indicator of the presence of significant MCA occlusions. It is less reliable for ACA or PCA disease as there is more variability in their normal anatomy.

In the present study, the blood velocity in the symptomatic MCA was usually abnormal when a proximal MCA main stem or major branch occlusion was expected from the clinical and CT brain scan findings. The accuracy in predicting likely MCA main stem or major branch occlusion was good at 86% in accordance with the previous studies. The accuracy in identifying a probably patent MCA was less good (60%), although the likelihood of having significant MCA disease in the presence of a normal symptomatic MCA blood velocity was low (NPV 89%). Reasons for failure to find an arterial signal, other than arterial occlusion, include displacement of the artery by swollen brain, poor operator technique, unco-operative or restless patient, and tortuous course of the MCA dipping down low into the temporal fossa out of the line of sight of the TCD probe. Great care is necessary to ensure that the failure to identify an MCA blood velocity signal is not simply due to any of these factors rather than the presence of MCA occlusive disease. Reasons for finding a "normal" symptomatic MCA blood velocity include early spontaneous recanalisation and persistent

branch occlusion with hyperaemic flow in the patent branches as described above. The closer the TCD examination to the onset of stroke symptoms, the greater the chance of finding a reduced MCA blood velocity. In the present study the "normal" MCA blood velocities in four of the patients with a TACI syndrome may have been due to either of these mechanisms.

The failure to identify any arterial signal in 11% to 13% of patients is also similar to that found in previous studies.^{128,141,153,154,159} The proportion of patients with dense temporal bone windows increases with age and represents a significant drawback to the use of TCD in acute ischaemic stroke patients.¹²⁸

TCD requires a skilled and experienced operator for correct performance and interpretation, particularly in acute ischaemic stroke. A radiological background is probably beneficial. Personal experience of teaching non-radiologists to do ultrasound shows that the lack of an inbuilt "3D image processing ability" (something only learnt with years of practice at cross-sectional imaging) is a serious disadvantage, even when performing cervical carotid Duplex ultrasound where there is a clear image to help orientation. TCD, with its reliance on the operator's skill and spatial awareness, and its lack of a guiding image, is more difficult and is unlikely ever to be available outside specialist centres. Colour flow TCD may help overcome some of these problems by

providing the guiding image, but even with the benefit of the grey scale image, colour flow TCD is still difficult, requires a skilled and patient operator, and the equipment is more cumbersome so less mobile than for spectral TCD.

2.4.5 The accuracy of the isotope Mean Cerebral Transit Time

In the present study, the MCTT was evaluated in a broad cross section of acute stroke patients and found to perform well in comparison with TCD. Despite including patients with impaired cardiac function and previous stroke, the MCTT appears to be a remarkably robust, simple and inexpensive technique. The accuracy in diagnosing likely MCA main stem or major branch occlusion was good (88%) and the MCTT seemed more sensitive to probable MCA small branch occlusions and PCA territory infarcts than TCD, the MCTT being more frequently appropriately abnormal in the patients with a PACI or POCI syndrome than TCD. The accuracy of the MCTT in diagnosing likely patent MCA was better than with TCD (90% with MCTT and 60% with TCD). The number of non-diagnostic studies (11% to 18%) was similar to the failure rate of TCD, and may decrease further with more experience of transit time patterns in acute ischaemic stroke. Problems were encountered in twelve of the patients in whom the cerebral transit time was generally prolonged, or there was loss of the normal anteroposterior gradient, but there was no asymmetry between the hemispheres. In six of these,

observation of the aortic and brain input curves during acquisition of data showed a slow rising, flat input curve indicating that the bolus had become dispersed and the result would not be valid. In the other six the input curve appeared relatively satisfactory on the computer screen so there was less warning that the data might be difficult to interpret. For this reason the latter six were included in the MCTT result "normal" when calculating the accuracy because this is an obvious area where errors in interpretation might occur. All apart from one of the twelve patients had evidence of a cardiac abnormality, and atrial fibrillation was by far the most frequent of these. Bilaterally prolonged transit and loss of the normal anteroposterior gradient may also reflect generally deranged cerebral blood flow in the acute phase of stroke, raised intracranial pressure, as well as cardiac impairment (primary or secondary to the acute stroke). Further study will be required to determine the true significance of these transit abnormalities.

The markers of cardiac or circulatory abnormality were chosen to be easily identifiable from simple history or clinical examination to act as warnings that the MCTT study should be interpreted with caution. Patients more likely to have a non-diagnostic MCTT study could thus be readily identified by simple criteria. Tight stenosis or occlusion of the ICA only caused problems in interpretation in one

patient because in the majority there was clear asymmetry on the arrival time image which was taken into account in interpretation of the transit time image. As more experience is gained with the transit time it should become easier to interpret these sort of results.

The present study has also suggested that the MCTT may be able to demonstrate cerebral arterial recanalisation as a shortening of the transit time. In the early validation studies³⁰⁹ concern was expressed that in the presence of extensive blood brain barrier breakdown, as would occur in all large infarcts, marked leakage of isotope into the extravascular space would occur during passage through the brain leading to artificially prolonged transit time. This might mean that it would be impossible to identify patients with extensive infarcts in whom the occluded artery had already (spontaneously) recanalised, as their transit would be similar to that of patients whose artery was still occluded. However the limited evidence presented here suggests that that will not be the case - recanalisation appears to be associated with a shortening of the transit time, possibly even to a faster transit in the symptomatic than in the asymptomatic hemisphere. However a further larger study will be required to examine the effect of recanalisation on the MCTT, to establish its reliability in diagnosing patients with large infarcts who have already recanalised their symptomatic artery.

The drawbacks to the MCTT technique in the present study were mainly due to the availability of isotope. 1200 MBq of isotope were delivered on weekdays for the study, which was sufficient for two doses in the morning, but only one dose if not used until the afternoon due to the decay of the isotope. A generator was available in the Department, but if old, it was not often possible to ensure that a sufficiently concentrated dose of isotope could be obtained. Too large a volume of injection would invalidate the MCTT examination. Problems were experienced with supply of isotope from Amersham for a three week period in the middle of the study. The Department of Nuclear Medicine operated an emergency only service on the same basis as the Department of Neuroradiology. These restrictions lead to exclusion of some patients from the study because they were admitted to hospital at the weekend, but most of these limitations could be easily overcome if the MCTT were an established clinical tool that could be justified on clinical grounds.

The hospital was spread over a large area, and the General Medical Wards, Nuclear Medicine and Neuroradiology Departments were separated by a good five minute walk and several lifts so it was sometimes difficult to justify moving a sick, confused patient on a separate journey for an MCTT on the days when the CT scanner was out of action or when it had not been possible to perform the MCTT at the same visit to the Neuroradiology Department as the CT scan.

Normally both tests would be done in the Neuroradiology Department on one visit. A map of the hospital is shown in Appendix Six, illustrating the geographical problems. The MCTT can be performed using a mobile gamma camera which, although rather cumbersome (like a 1970's portable x-ray machine), could be kept in the medical ward or acute stroke unit thereby reducing delays in investigation.

The MCTT was easy to perform and required minimum patient cooperation. The patient could be kept comfortable while preparations were made for the study, then put into the imaging position with the neck extended just for the acquisition phase (approximately 30 seconds), then quickly moved back to a more comfortable position. Many of the MCTT tests in this study were performed single handed. This was satisfactory when the patient was cooperative, but two persons were required for restless patients. If the MCTT was to be adopted more widely, it would probably be based in Nuclear Medicine or General Radiology Departments where there would be two persons for the short time required for the study. The isotope used in this study, technetium^{99m} pertechnetate is inexpensive and readily available. Minimum operator training is required for correct performance and interpretation of the MCTT study. All of this contrasts with the other currently available non-invasive methods of evaluating cerebral perfusion - SPECT with HMPAO or equivalent, PET, XENON CT, XENON radioisotope methods - all of which use

more expensive tracers, take more time, require more patient cooperation, use more expensive equipment and are simply not practical for the widespread, rapid investigation of a disease as common as acute ischaemic stroke. Also, although all these methods assess cerebral blood flow, they do so indirectly, and some are non-quantitative. SPECT with HMPAO may overestimate hyperaemia in infarcted tissue.³⁰² Although non-tomographic, the MCTT by rapidly measuring cerebral perfusion reserve, may be giving more useful information, than simply measuring cerebral blood flow. Cerebral blood flow on its own does not give enough information about the state of the cerebral circulation - information on cerebral blood volume is also important.

If in the future any treatments for acute ischaemic stroke are to work then it is likely that they will have to be administered with minimum time delay, so any necessary pretreatment imaging tests have got to be simple, rapid and practical. The MCTT is inexpensive, and gamma cameras are already available in many District General Hospitals as well as teaching hospitals. A high sensitivity collimator, a hand-held scintillation counter, a simple interface to link to a micro computer (IBM or equivalent - an old BBC was used in this study) plus appropriate software is all that would be required. It is by far the most promising and practical method so far of assessing cerebral arterial occlusion in acute ischaemic stroke so far available.

2.4.6 On the comparison of the absolute values of middle cerebral artery blood velocity and hemispheric mean transit time

The present study concentrated on the pattern of transit abnormality rather than on the absolute values of the transit time because the aim was to test the MCTT as a simple, rapid, unsophisticated diagnostic test to answer the simple question "is there a major arterial occlusion or not?" The MCTT had not been widely tested in patients likely to have impaired cardiac function and it was uncertain what impact including such patients would have on the interpretation of the results. It therefore seemed appropriate to concentrate on the colour pattern of the MCTT result rather than on the absolute values. Patients with cardiac abnormalities caused fewer problems than anticipated, so a limited examination was made of the relationship between the absolute values of transit time and the blood velocity in the MCAs. Previous studies have shown the reciprocal of the hemispheric transit time is directly proportional to the arterial blood velocity - the faster the blood velocity the shorter the transit time.^{214,309} Both TCD and MCTT give an index of velocity flow within the cerebral circulation. Velocity flow is proportional to the second power of the vessel radius whereas volume flow is proportional to the

fourth power of the vessel radius. Previous studies have also demonstrated a non-linear relationship between MCA blood velocity and perfusion³²² and cerebral transit time and perfusion³²³ in addition to the validation studies by Naylor, Merrick et al.^{214,309} This suggests that changes in MCA blood velocity, in these studies, were due to changes in the volume of blood passing through the artery assuming that there was no change in the arterial radius or length. One angiographic study showed no change in the calibre of the MCA during hypo- and hyper-capnoea³²⁴ but angiography may not be a very accurate way of measuring arterial calibre. Even as little change in arterial calibre as 10% may result in a 36% change in the resistance to flow. More recent evidence from carefully controlled TCD studies has suggested that there may be changes in MCA diameter with posture in normal individuals as part of the autoregulatory response.¹⁴⁶ It is therefore probably not valid to assume that the MCA diameter remains constant under physiological conditions. Further study is required to evaluate this relationship in the light of new information on the behaviour of the basal intracranial arteries under physiological conditions.

In the present study, the MCA blood velocity was proportional to the reciprocal of the transit time in the symptomatic but not in the asymptomatic hemisphere. This discrepancy may be because when the cerebral circulation is

functioning normally, as it might be in the asymptomatic hemisphere, that there may be a range of blood velocities for any given transit time. It may be that it is only when the cerebral circulation is stressed, as in the symptomatic hemisphere, that the relationship between falling blood velocity and prolonged transit time becomes apparent. The study by Naylor et al examined the relationship between transit time and blood velocity during hypo- and hypercapnoea, not at rest.^{214,309} In 32 carefully selected patients with first-ever acute ischaemic stroke and no evidence of cardiac impairment, Naylor et al's findings were similar to those in the present study, though the difference in the closeness of the relationship between blood velocity and transit time in the symptomatic and asymptomatic hemispheres was less obvious.³⁰⁹ It may be that the results in the present group of 85 patients were diluted by inclusion of the patients with the bilaterally prolonged transit as the latter reflected impaired cardiac function and was nothing to do with the cerebral circulation. It may also be that a more comprehensive control population is required to examine more closely the relationship between transit time and age. In the original validation study²⁰⁵ no relationship was found with age in the 102 "patient controls" but they may have been a younger, generally healthier age-group (their age was not specified) than the age-group typically affected by acute ischaemic stroke, and at extremes of age

there may be a relationship between age and prologation of the transit time. Examination of the relationship between age and transit time in the asymptomatic hemisphere in the patients in the present study certainly suggested that there may be an important relationship, but this may have been because cardiac abnormalities increase in frequency with age leading to greater likelihood of a prolonged transit time. Further study of this specific patient group is required to clarify the importance of this observation.

2.4.7 General points concerning the imaging investigation of patients with acute ischaemic stroke

At the present time, in the United Kingdom at least, access to imaging investigations for acute stroke patients is generally restricted and poor. Many physicians caring for patients with an acute stroke are frustrated by the lack of availability of CT scanning for their patients (personal survey of members of the British Stroke Research Group). Until recently, CT scanners were regarded as a relative luxury, rather than as a basic workhorse for neuroimaging as in the USA. This reflects differences in health care funding and general lack of resources, or failure to target resources effectively, in the UK. As it is generally perceived that there is no treatment for acute ischaemic stroke, it is also commonly thought that there is no point in doing inves-

tigations to diagnose the cause of the stroke. However now that there are secondary prevention treatments of proven benefit in acute ischaemic stroke, it is important to diagnose the cause of the stroke in patients being considered for carotid endarterectomy, aspirin or anticoagulant therapy to use these treatments effectively. It is generally perceived that patients being considered for secondary prevention can be investigated in the second or third week after symptom onset - there is no need to perform investigations rapidly and a reasonable number of acute stroke patients may actually have a CT brain scan at some point after the acute event (it is not known how many) though not within 24 hours. This may or may not be an appropriate way to manage these patients, but if the primary treatment of acute ischaemic stroke is ever to advance, it is likely that investigations will need to be performed as soon as possible after symptom onset so that treatment can be started as soon as possible to limit ischaemic brain damage.

Parallels can be drawn with the progress which has been made since the early 1960s in the hospital care of acute myocardial infarction patients. Prior to the 1960s many MI patients were cared for at home as there seemed little point in sending them to hospital if nothing could be done. Then with the development of pacemakers and drugs to treat arrhythmias, hospital care was perceived as offering some benefit. Coronary care units were established associat-

ed with the idea that acute MI patients had to reach hospital quickly for maximum benefit. Once the network of CCUs was established, it then became relatively easy to test treatments such as thrombolysis, beta blockers, calcium antagonists. But it has taken nearly thirty years to arrive at this level of sophistication for acute MI patients, and doctors are still looking for ways of getting patients to hospital faster and optimising use of hospital facilities. Care of acute ischaemic stroke is at a similar stage to care of acute MI in the early 1960s. There are a lot of organisational problems to be overcome before any acute stroke treatments can be effectively delivered to the correct patients. The major differences between acute MI and acute stroke are that a) the diagnostic test for acute MI, the ECG, is mobile, cheap and quick, whereas a CT scanner is static and expensive, and b) acute MI patients can complain loudly until someone does something about their chest pain, whereas many acute stroke patients cannot complain at all!

The layout of the Western General Hospital is probably fairly typical of many UK hospitals and illustrates some of the logistic problems encountered in trying to investigate patients rapidly. There are long distances between departments involved in the care of stroke patients (Appendix 6) with poor access to lifts and hospital porters. In many hospitals there is no dedicated team of professionals to care for the stroke patients although many hospitals are

now setting up acute stroke units to rectify this. There is increasing evidence that acute stroke units benefit the patient by reducing time in hospital and improving patient independence after discharge.³²⁵ Therefore the investigation of acute stroke patients has to be kept as simple as possible to counteract the complexities already present in the hospital system.

It is clear therefore that there is no longer any place for a nihilistic attitude towards investigation of acute stroke patients. The first step must be to diagnose the cause of the stroke and CT scanning is the best commonly available method for this. It may not be possible to make a positive diagnosis of ischaemic stroke with CT, but it will exclude intracerebral haemorrhage, tumours, and infection reliably. It is not possible to differentiate reliably clinically between these diseases. Scanning the patients in the present study caused a certain amount of friction in the Neuroradiology Department - acute stroke patients were perceived as causing a major increase in the number of patients scanned resulting in a doubling of the outpatient waiting list and in the out of hours workload. In fact the number of acute stroke patients scanned in proportion to the total number of patients going through the CT department was very small, with no increase in out of hours work, but stroke patients drew a disproportionate amount of attention to themselves as they were often sent without a nurse escort

and needed extra nursing attention while in the Department. Simple measures such as ensuring that a nurse came with the patient, that the patient was on a trolley not in a wheel chair if they were unable to weight-bear, and that the patient was referred to CT scanning as soon as possible (not, for example, at 1600 hours when they had been in the hospital since 1000 hours) helped ensure the smooth running of the CT service with good access for stroke patients. There is plenty of room for improvement in the 0900 to 1700 provision of CT scanning for stroke patients before worrying about the out of hours service.

A patient with suspected acute ischaemic stroke should have a careful clinical examination to define the likely site and extent of the infarct and underlying arterial occlusion followed by a CT brain scan to exclude tumour or PICH. If in future treatments become available which are dependant on the type of arterial occlusion, for example thrombolysis, then an assessment of cerebral perfusion could be made using the MCTT or TCD. Equipment to perform these could be sited either near the CT scanner or the acute stroke ward. Many of the treatments under trial for acute ischaemic stroke at the moment such as aspirin, heparin, thrombolysis, glutamate antagonists, free radical scavengers, etc, have serious and unpleasant side effects and so the ratio of beneficial to adverse effects may depend on the type of ischaemic stroke. For example in a patient with a

lacunar stroke whose prognosis is good without any treatment should probably not be exposed to a treatment with beneficial but also serious adverse effects, whereas in a patient with a TACI syndrome whose prognosis is so bad the treatment may be worth while.

In conclusion, the MCTT may be sufficiently accurate and practical to be the rapid, widely available diagnostic test for the likely site of arterial occlusion in patients with acute ischaemic stroke. It may also be extremely useful in research into the natural history of acute ischaemic stroke, and in the assessment of the action of novel drugs in acute ischaemic stroke.

Summary of Part Two

1. The need for a rapid method of diagnosing cerebral arterial insufficiency in acute ischaemic stroke is discussed.
2. The methodology of the study to evaluate the accuracy and practicality of the isotope Mean Cerebral Transit Time (MCTT) is discussed, using a combination of clinical examination and CT brain scan findings as the "surrogate gold standard" for the site of infarction, and Transcranial Doppler ultrasound as an alternative non-invasive diagnostic tool against which to test the isotope MCTT.
3. The Oxfordshire Community Stroke Project clinical classification of acute stroke syndromes was found to be accurate in predicting the site of cerebral infarction as diagnosed by CT brain scanning.
4. A simple classification of cerebral infarcts as seen on CT brain scans was found to have excellent interobserver agreement, and to be a reliable way of differentiating between similar sized infarcts with different amounts of swelling in the acute phase.
5. The accuracy of TCD in diagnosing the likely site of cerebral arterial occlusion was similar to that described in previous studies of patients with acute ischaemic stroke.
6. The accuracy of the MCTT is similar to Transcranial Doppler.
7. The main drawback of the MCTT is its dependance on good cardiac function for a diagnostic study although this caused

problems in surprisingly few patients. Patients in atrial fibrillation were most likely to have a non-diagnostic MCTT study.

8. The MCTT is a less operator dependant technique than TCD, is as quick or quicker, and the facilities to do it are already available in many District General Hospitals.

9. General problems encountered in ensuring that acute stroke patients are investigated appropriately and rapidly, given that hospital and particularly CT resources are limited, are discussed.

Part Three

The Relationship Between Cerebral Blood Flow and Formation of Oedema in Large Acute Ischaemic Strokes - Does Early Reperfusion of the Cerebral Infarct Worsen Cerebral Infarct Oedema Formation or Final Clinical Outcome?

Part Three

Chapter One

Does Early Reperfusion of the Cerebral Infarct Worsen Cerebral Infarct Oedema Formation or Clinical Outcome?

Introduction and Background Information

3.1.1 Aim of the study

3.1.2 Introduction

3.1.3 The mechanism of ischaemic cerebral oedema formation and the relationship to reperfusion - results of experimental work and a summary of the limited information available from stroke patients.

3.1.1 Aim of the study

The aim of this study was to examine prospectively the relationship between blood flow to the infarcted cerebral tissue in the first few days after stroke onset, and:

- 1) the amount of swelling in the infarct; and
- 2) the final clinical outcome.

The hypothesis being tested is that an increase in blood flow to the ischaemic or infarcted brain lessens (or at least does not worsen) the amount of infarct swelling in the acute stage, and leads to a better clinical outcome. Clearly, if reperfusion of the infarct led to worse infarct swelling and a poorer clinical outcome, there would be little point in testing thrombolytic (or possibly antithrombotic) drugs in acute ischaemic stroke where the intended mechanism of action is to improve infarct perfusion.

3.1.2 Introduction

Cerebral infarction is always followed by oedema formation in the infarcted tissue (apparent microscopically though not always macroscopically), as part of the response to injury.³²⁶ This may cause the infarct to swell, compress surrounding brain and possibly damage otherwise viable neurones at the margins of the infarct by impeding their blood supply further. If severe, a cerebral hemispheric infarct may swell so much that tentorial herniation occurs, and the patient dies of brain stem compression in the first few days after the stroke.²⁴⁶

The influence of early reperfusion of the infarct on infarct swelling is unclear, there being conflicting results from experimental work^{52,327,328,329,330} and little information from stroke patients.^{61,276,298,331,332} Experimental models, discussed in more detail in the next section, are useful but the results should not be extrapolated directly to stroke patients.⁵⁷ There are many examples of new drug treatments for stroke, which appear promising when tested in animals, but have no beneficial effect, or unsuspected adverse effects, in stroke patients.⁷⁰ Koudstaal et al³³¹ in 1988 described two patients who developed massive cerebral infarct oedema and died following intravenous thrombolytic therapy for acute ischaemic stroke. One patient dying two and a half days after the stroke had patent cerebral arteries at post mortem, but there was no information on the

patency of the other patient's arteries. Koudstaal et al concluded that "Thrombolytic treatment.... started three to four hours after a major ischaemic stroke may be hazardous, not because of haemorrhagic transformation but because early reperfusion may promote massive, potentially fatal cerebral oedema". This anecdotal but high-profile report has been cited as a good reason for not attempting to improve blood supply to acute ischaemic strokes in the acute phase. Part of the difficulty in examining the relationship between blood flow to and swelling in cerebral infarction has been, until recently, the lack of readily available non-invasive blood flow imaging techniques.

CT brain scanning has been available for longer, and there have been several studies of the change in appearance of cerebral infarcts on CT scanning with time which have noted that swelling of the infarct occurs in the first week, followed eventually by atrophy.^{265,266,248,305,333} These studies examined mass effect or made serial volume measurements of the infarct, but did not attempt to distinguish the site and extent of the infarct from the effect of swelling. Also, there have been no prospective studies which have tried to assess causes of cerebral infarct swelling in stroke patients. There is also little information on the frequency of severe infarct swelling, or on whether increasing blood flow to the infarct in the first few days after onset improves or worsens outcome.

Until recently, lack of practical non-invasive imaging techniques for assessing cerebral blood flow hampered attempts to study the pattern of cerebral arterial occlusion in acute stroke patients. However TCD is now an established method which can be used with minimal disturbance to the patient (see Part 1.4). Although Doppler ultrasound measures blood velocity and does not measure blood flow directly, the adequacy of the blood supply to an area of brain can be inferred from the velocity signal. TCD has been used in studies to monitor cerebral arterial patency following acute ischaemic stroke.^{125,253,298,299} A normal blood velocity in the MCA main stem (M1 segment) implies "good" flow to the MCA territory even if one of the main branches is blocked, compared with a velocity reduced to half or even less of that in the asymptomatic MCA with the identical anatomical lesion, which implies "poor" flow to the MCA territory. A velocity increase in the symptomatic MCA main stem during the first week after stroke from barely detectable to a near normal TCD signal implies that the flow in the MCA has "improved", whether due to recanalisation or to persistent occlusion with hyperaemic flow in the patent branches feeding collaterals at the margins of the infarct (Figure 1.4.2). Furthermore, a normal or near normal symptomatic MCA blood velocity with 24 hours of stroke in a patient with symptoms of extensive MCA territory ischaemia, would be compatible with: 1) early recanalisation of an MCA main stem

occlusion; 2) persistent occlusion of a major branch of the MCA with increased flow in the patent branches giving a net "normal" or near-normal blood velocity in the main stem; or 3) occlusion of one or more minor branches of the MCA (either the primary cause of the stroke or due to fragmentation and migration of an embolus). These possibilities are indicated schematically in Figure 1.4.2. As long as very simple criteria are used to define blood velocity, the conditions under which the measurements are made are carefully controlled and only large increases or decreases in velocity (excluding focal stenoses) counted as change, then it is reasonable to infer blood flow changes from blood velocity changes.

Now that non-invasive imaging tools are available, with reasonably well understood limitations, it is feasible to study acute infarct swelling prospectively, without undue disturbance to the patient, taking advantage of the tendency of the occluded cerebral artery that caused the stroke, to recanalise spontaneously (see Part 1.1, Part 1.3 and Figure 1.3.1). Up to 20% of large cerebral artery occlusions may recanalise spontaneously within 24 hours, increasing to possibly 80% by the end of one week after stroke onset.^{115,117-120,122,123,125}

3.1.3 The mechanism of ischaemic cerebral oedema formation and the relationship to reperfusion - results from experimental work.

The sequence of events leading to cellular ischaemia and death following interruption of the blood supply to part of the brain has been studied in primates and other mammals.^{51,334} As blood flow decreases, progressively more cell homeostatic functions fail (Figure 3.1.1). Following complete and sudden interruption of the blood supply, electrical activity of the neurones stops in a few seconds, followed by failure of the sodium pump and glucose depletion.³²⁶ Intracellular oedema, mostly derived by fluid movement from the extracellular space into the cells, is evident after a few minutes and there is a massive rise in tissue lactate.⁵³ Up to this stage, the process is potentially reversible, but thereafter a stepwise sequence of organelle failure occurs as thresholds for survival are reached and passed. The same impairment in cerebral blood flow, in mls per 100 grams of brain per minute, is associated with a similar degree of cell malfunction in all mammals tested (cats, gerbils, baboons), and it is reasonable to assume that similar levels would apply in humans.⁵² The preservation of some circulation might prolong the time taken for this sequence of events to occur, and provided the blood hydrostatic pressure remains low in the infarct, the blood brain barrier remains intact and there is virtually no

leak of protein from the intravascular to extravascular space.^{328,335,336} Note that, as shown in Figure 3.1.1, cellular oedema formation begins prior to irreversible cell damage, at a higher threshold than calcium and potassium pump failure in the cell membrane.

Although the response to reduced blood flow is similar within and between species at the cellular level, the response, in terms of decrease in blood flow in the arterial territory following acute cerebral arterial occlusion, is very variable between individuals. Experiments in monkeys have shown that distal to an MCA main stem occlusion the blood flow decreases to 25 percent of normal.³³⁷ Autoradiographic blood flow studies in animals have shown flows which range from near zero to near normal values in the territory of an occluded vessel.²³⁶ Therefore it is probable that some blood flow usually persists distal to a major cerebral arterial occlusion, supplied via the collateral circulation, which slows down the development of the infarct and may even arrest the process at any stage. This variation in blood flow distal to an apparent MCA occlusion could explain the observation of reduced but clearly measurable, blood velocity with TCD in stroke patients distal to an angiographically proven MCA occlusion.¹³⁸

Other experimental work has shown that the presence of venous obstruction (as well as arterial) worsens the ischaemia. Ischaemic damage and swelling are less if the veins are

patent, and less still if the ischaemic tissue is perfused with saline during arterial occlusion.³²⁹ These experimental results imply that both stasis and accumulation of metabolites are important factors in ischaemic damage.³²⁶ Reduction in systemic blood pressure may further worsen the ischaemic insult.³³⁸ Other factors which may contribute to ischaemic cerebral oedema formation include systemic hypertension³³⁵ and hyperglycaemia,³³⁹ though in both cases the evidence of cause and effect is conflicting, ie are hypertension and hyperglycaemia simply the consequences of a severe stroke, or vice versa. In stroke patients two factors which might also affect infarct swelling are the age of the patient and the plasma albumin. It is possible that younger patients might have a more aggressive response to tissue injury, or that they might have less room for infarct swelling which would correspondingly appear more severe. A low plasma albumin might encourage leakage of fluid from the intra- to extravascular space and increase infarct swelling. These latter two factors are purely hypothetical.

The development of cytotoxic oedema is followed by vasogenic oedema, which is secondary to breakdown of the blood brain barrier with leakage of protein and water into the extracellular space. It has been shown to be maximal at seven to ten days in rhesus monkeys,³³⁶ corresponding with the time of maximal contrast enhancement of infarcts on CT brain scans in stroke patients.²²⁷ The time of maximal

oedema formation in monkeys is four days,³³⁶ and in humans three to five days²⁶⁵ (based on CT brain scanning and autopsy data), though in smaller mammals it occurs earlier.³²⁶ The period of maximal infarct swelling is therefore likely to be due to a combination of intra and extracellular oedema.

The earliest sign of cerebral infarction on a CT brain scan is decreased density in the ischaemic or infarcted tissue,²²⁹ shown in animal experiments to indicate oedema formation.³⁴⁰ It is therefore conceivable that in the territory of an occluded MCA, one might see cerebral oedema formation on a CT brain scan, in the hours after stroke onset, indicating ischaemic but not irreversibly damaged tissue.

Although the blood brain barrier is intact to large molecules up to several days after the onset of ischaemia, it may be leaky to water, and evidence from several animal experiments suggests that reperfusion of the occluded artery after ischaemic damage has occurred is associated with a massive rise in extracellular water and worse oedema than if the artery had remained occluded.^{330,341} For example, in gerbils restoration of blood flow within an hour of ischaemia caused a reduction in the brain water content, whereas if restoration of flow is delayed until three hours, there is a massive rise in brain water content.³²⁷ Symon et al³²⁸ found that reperfusion after 30 minutes of MCA occlusion in

monkeys was not associated with any significant increase in brain water content, whereas reperfusion after 90 minutes of occlusion was associated with an increase in water content where the reperfusion had occurred. Bell et al⁵² showed that in baboons, the cerebral blood flow threshold for oedema formation is 40% of normal, and that flow levels less than this can be tolerated for up to 30 minutes without permanent damage being sustained. Reperfusion after 30 minutes of ischaemia was not associated with any increase in brain water content, but reperfusion after 100 minutes of ischaemia was associated with increased brain water content particularly in grey matter. Sundt et al³⁴² found that restoration of blood flow after three hours of MCA occlusion in squirrel monkeys or six hours in cats reduced infarct size but that oedema was slightly worse in the cerebral infarct following reperfusion than in those animals without reperfusion. Crowell et al³⁴³ found that deficits from ischaemia were commonly reversible after 30 minutes and four hours of MCA occlusion in monkeys, but rarely reversed after eight hours or more of occlusion. Other experiments in rats have suggested that reperfusion in the first few hours following ischaemia is associated with greater damage to the cerebral arteriole endothelium on microscopy (than persistent arterial occlusion) leading to greater permeability to plasma constituents and brain oedema.³⁴¹ One possible mechanism of "early reperfusion injury" is increased calcium ion flux

into the ischaemic neurones.^{344,345}

The brain can survive mild ischaemia for some time, but is intolerant of profound ischaemia for even short periods, so that the depth and not just the duration of ischaemia are both important factors.³²⁸ The greater and longer the decrease in cerebral blood flow, the greater the amount of ischaemic damage and brain oedema.

A further factor to be considered is whether early reperfusion of ischaemic tissue (with apparently favourable early symptomatic response) may be followed by "delayed reperfusion injury" with progressive neurological deterioration occurring one to two weeks later.⁵⁸ Three case reports and two experimental studies referred to by Caplan⁵⁸ concern sequelae of global cerebral anoxia not focal acute cerebral infarction. The mechanism and pathophysiology of global cerebral ischaemia may be quite different to focal ischaemia.⁵⁷ There is no evidence as yet that "delayed reperfusion injury" occurs following acute focal cerebral ischaemia.

There is scant information on the relationship between reperfusion and infarct swelling in stroke patients, most obtained indirectly from studies designed to address other issues. The anecdotal report of two patients by Koudstaal et al³³¹ has already been mentioned in the Introduction to Part Three (3.1.2). Ogata et al⁶¹ suggested that ischaemic cerebral oedema was worse in acute ischaemic stroke patients whose ICA or MCA remained occluded (on

angiography), than in those who reperfused early. Overgaard et al described three patients treated with thrombolytic drugs following acute ischaemic stroke (whose occluded arteries did not recanalise) who developed severe fatal cerebral infarct oedema.³³² Mori et al²⁷⁶ in a trial of intravenous thrombolysis in acute carotid territory ischaemic stroke, found severe infarct oedema with mass effect was more frequent in patients whose artery remained occluded on angiography (7/20) than in those who reperfused (1/11).

Several other recent reports have examined the relationship between reperfusion and clinical outcome. Ringelstein et al,²⁹⁸ using TCD and angiography, showed that haemorrhagic transformation of the infarct was more frequent and clinical outcome much worse in patients whose symptomatic arteries remained occluded than in those whose arteries recanalised. Moulin et al³⁴⁶ found that 5/9 patients with recanalisation (shown angiographically) following thrombolysis recovered to live independantly by one month after onset (none died), compared with only 1/9 with no recanalisation (four died). Baird et al,³⁴⁷ in a pilot study of thrombolysis, found that reperfusion (measured by SPECT) correlated with significant neurological improvement, whereas patients with persisting hypoperfusion made a poor neurological recovery.

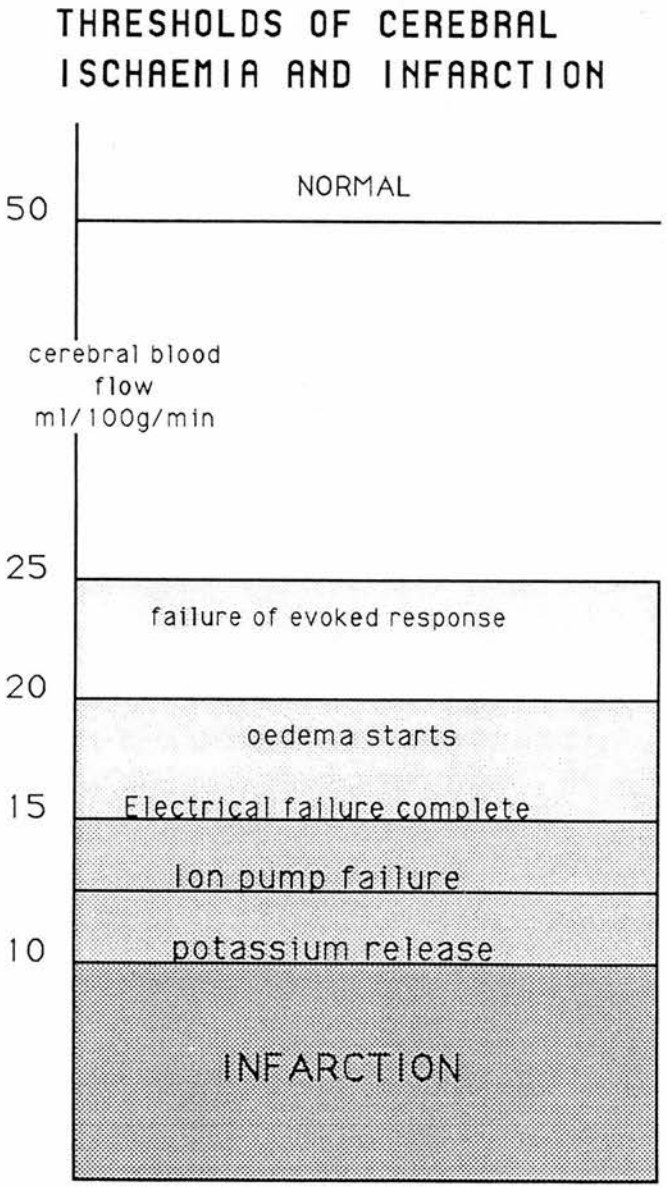
These results in stroke patients conflict with the experimental results, as the experimental studies suggest

that treatments aimed at improving perfusion to an infarct might be detrimental if not initiated very early, ie within 30 minutes of symptom onset. This is obviously impractical in stroke patients. However the results of some of these experimental models may not be directly applicable to man.⁵⁷ Tthe experimental studies also disagree on the duration of ischaemia that can be tolerated. The important questions are: 1) whether any increased damage due to "reperfusion injury" is counterbalanced by benefit in terms of salvage of ischaemic but viable neurones by reperfusion; and 2) for how long after the onset of ischaemia will reperfusion be beneficial? The answer to both questions must probably await the result of large trials of reperfusion vs no reperfusion (by therapeutic means) in stroke patients. It is however an important point to resolve, as at present much time and effort is being expended on testing acute ischaemic stroke treatments specifically intended to increase tissue perfusion, namely thrombolysis, aspirin and heparin. These would obviously be contraindicated if they were only to make matters worse. The disagreement among the experimental studies on the tolerable duration of ischaemia, and the indirect evidence suggesting likely benefit of reperfusion in stroke patients (all at various time windows up to 24 hours), provide strong arguments for assessing acute stroke treatments at different time intervals after stroke, and not just adopting a rather empirical six hour onset-to-treatment

cut off.

As the relationship between cerebral blood flow and infarct oedema is controversial and poorly understood in man, and is fundamental to the understanding and development of treatments of acute ischaemic stroke, a study was set up to examine this prospectively in patients with symptoms of extensive cerebral infarction in the MCA territory, using non-invasive imaging techniques.

Figure 3.1.1 Thresholds of cerebral ischaemia and infarction - the Ischaemic Penumbra The cerebral blood flow thresholds for failure of neuronal function are shown on the y axis. Similar thresholds have been found in all mammals tested, so it is likely that the same thresholds apply in stroke patients. (50,51,54)



Part Three

Chapter Two

Does Early Reperfusion of the Cerebral Infarct Worsen Cerebral Infarct Oedema Formation or Clinical Outcome?

Patients and Method

- 3.2.1 Study population
- 3.2.2 Clinical identification and classification of patients
- 3.2.3 Clinical follow up
- 3.2.4 Timing of imaging studies
- 3.2.5 Imaging studies - CT brain scanning
- 3.2.6 Imaging studies - transcranial Doppler ultrasound
- 3.2.7 Consent for imaging studies
- 3.2.8 Statistical analysis

3.2.1 Study population

As many patients as possible admitted to the Western General Hospital between 25.11.90 and 31.08.92 within 24 hours of onset of extensive acute ischaemic stroke in the MCA territory were included in the study. These were therefore patients with either a TACI or "large PACI" acute ischaemic stroke. A TACI syndrome indicates ischaemia or infarction of a large part or all of the MCA territory, and consists of the triad of a) hemiparesis affecting face, arm and leg, 2) hemianopia, and 3) new higher cerebral dysfunction (for example dysphasia or neglect). A "large PACI" suggests ischaemia or infarction of at least half of the MCA territory and consists of two of the triad of signs for a TACI. The diagnostic criteria for TACI and PACI are described in detail in Part 2.2, and in Appendix 2. Patients with symptoms suggestive of less extensive ischaemia were excluded as it might be more difficult to measure the infarct size on CT scans and because they would be less likely to have abnormal MCA blood velocities.

Patients with first ever stroke and recurrent stroke were included, but only if the previous stroke had been minor (minor, non-disabling anterior or posterior circulation infarct). There was no upper age limit for inclusion, although patients below the age of 18 were excluded. Patients were also included regardless of their drug treatment

before and after the stroke, regardless of other concurrent illness and regardless of the suspected cause of the cerebral infarct. Patients were included in the study as long as they or a close relative and attending physicians gave their consent for participation, and as long as it was considered ethical for that particular patient to be included in the study.

3.2.2 Clinical identification and classification of patients

Patients were identified by Dr Martin Dennis during the North Lothian Stroke Survey (NLSS), or Dr Richard Lindley after the NLSS, as described in Part 2.2. All patients had a thorough clinical examination as soon as possible after admission (but within 24 hours at most) and careful history was obtained of stroke risk factors, past medical history and time of stroke onset, either from the patient or a close relative or friend. In patients who awoke with a stroke, the time of onset was taken to be midway between the time of going to sleep and time of waking. If the patient was found collapsed with the stroke unable to give a history, then the time of onset was estimated from knowledge of when the patient was last seen prior to the stroke, and what the patient appeared to have been doing at the time of the stroke (for example eating breakfast, or getting dressed). No attempt was made to change referral patterns or speed of referral of patients to hospital.

The patient's plasma glucose and haemoglobin were measured within 24 hours of admission to hospital, and plasma albumin within one week of symptom onset.

3.2.3 Clinical follow up

Outcome was assessed at one and three months after the stroke as: 1) dead; 2) no improvement neurologically from the time of admission with the stroke; 3) improving neurologically but still in hospital; 4) in long term care; 5) in rehabilitation (aiming to go home eventually); or 6) home. This information was obtained from ward staff if the patient was still in hospital, from the NLSS or Streptokinase Trial follow up done by one of the members of the Department of Clinical Neurosciences, or from the patient's GP. The scale was very simple to apply, and although it did not take account of the patient's disability relative to their social circumstances, it did allow simple differentiation between death and severe disability on the one hand, and independent living on the other.

2.2.4 Timing of imaging studies

All patients had a CT brain scan and TCD examination as soon as possible after admission ("0 to 2 day" examination). Two more CT brain scans were performed in surviving

patients. The second CT brain scan was between three and seven days (as near to three to four days as possible - "3 to 7 day" examination), and the third between eight days and three weeks (as near to fourteen days as possible - "14 day" examination) after the stroke onset. The exact timing of the CT scans was, to some extent, determined by clinical factors and practicality in a busy Neuroradiology Department. It was hoped that the second CT brain scan would show the maximum infarct swelling, as previous studies have suggested that maximum swelling occurs between three and five days after symptom onset.^{248,265,266} The third CT brain scan was done to examine the duration of infarct swelling, and to look for change in the extent of the infarct from the admission CT brain scan.

TCD studies were done daily in the first week, twice in the second week, and once in the third week.

As many patients as possible had a carotid Duplex ultrasound examination to look for significant carotid disease in the neck such as tight ICA stenosis or ICA occlusion. This was to provide corroborative evidence to back up the TCD findings.

Some patients died or were considered too ill to move (for non-neurological reasons, for example unstable cardiac status following an acute myocardial infarct), or were discharged prior to completing the three weeks of imaging. All available data on all the patients has been included.

3.2.5 Imaging studies - CT brain scans

The CT brain scans were performed in the axial plane, at ten millimeter intervals, without radiographic contrast, using an IGE 8800 CT scanner with a fast image processing upgrade. The entire brain was examined.

The CT brain scans were reviewed blind to the clinical information, and blind to all other CT brain scans for the same patient, by two neuroradiologists, Dr R Sellar, Consultant, and myself. The CT scans were examined for the presence of a recent infarct and then coded for the site and extent of the recent infarct, the amount of swelling in the recent infarct, and the presence of any haemorrhagic transformation (Figures 2.2.1a - c). A recent infarct was identified as an area of decreased density relative to normal brain (often best appreciated by comparison of the brain densities in equivalent parts of the two hemispheres) conforming to an arterial territory as described in Part One Chapter Six. Signs such as loss of the normal outline of the lentiform nucleus,²²⁹ loss of the insular ribbon,²³⁰ and loss of the normal grey-white matter differentiation were particularly sought.²²⁸ Recent infarction was usually associated with some mass effect causing loss of visibility of the cortical sulci when minor, to midline shift and effacement of the basal cisterns when massive. The maximum amount of swelling in the infarct was simply the largest amount of

swelling seen on any of the patient's CT brain scans (usually the second one). The extent of the infarct was taken as the maximum extent seen on any of the scans. An old infarct (ie older than three months) was identified as an area of marked low density compared with surrounding brain associated with atrophy of adjacent structures. A haematoma was identified as a rounded area of increased density relative to normal brain associated with mass effect. The presence of any haemorrhagic transformation of the infarct was noted to ensure that any increase in infarct swelling was not simply due to the development of a large focal haematoma within the infarct. This study was not designed to examine the relationship between blood velocity changes and haemorrhagic transformation. Larger numbers of patients would be required to do that, and it would be more appropriate to examine all ischaemic strokes, not just large ones.

The codes used to describe infarct site/extent, swelling and haemorrhagic transformation were the same as those described in Part Two, Chapter Two and found to have "excellent" interobserver agreement for infarct site/extent for large infarcts and for infarct swelling when tested for interobserver reliability (Part Two, Chapter Three). For infarct site/extent only the codes describing infarcts in the MCA territory were used (codes "10" to "80") therefore the zeros were omitted (ie the codes became "1" to "8"). Where there was any disagreement on coding of the infarct

appearance, the scan was discussed and an agreement reached. It was not necessary to obtain a third opinion on any scan. The codes are also listed in Appendix Three.

3.2.6 Imaging studies - transcranial Doppler ultrasound

The TCD studies were performed blind to all clinical information apart from the name of the patient and the side of the infarct. The result was interpreted and recorded on the patient's record sheet before the results of other imaging tests were known.

An Eden Medical Electronics TC 64B ultrasound machine with 2 MHz hand-held probe was used, as described in Part 2.2. Recordings of the peak and mean blood velocities were obtained from the MCAs (65 to 35 mm depth), ACAs (65 to 75 mm depth) and PCAs (60 to 80 mm depth) through the temporal bone windows, and of the ICAs and ophthalmic arteries through the orbits.¹²⁸ Where the symptomatic MCA was undetectable, clear signal from the ipsilateral ACA or PCA had to be obtained to ensure that failure to detect the MCA was due to occlusion of its origin and not due to failure of the technique. Patients in whom it was impossible to obtain a signal from any one of the basal intracranial arteries were considered to have a poor temporal bone window and excluded from the study.

The mean blood velocity (time averaged mean) in the

symptomatic MCA was expressed as a proportion of the mean blood velocity in the asymptomatic MCA using the coding system described in Part 2.2 and Appendix Four. The ACA and PCA blood velocities relative to the asymptomatic side (normal, increased or decreased) and direction of flow in the ACA and ophthalmic artery (normal or reversed) were also expressed using the coding system. The coding system was very useful because it enabled the often complex relationship between blood flow velocities in the major arteries in the base of the brain to be condensed into a three digit numeral which could also be used to describe changes in the blood flow velocity with time. A difference in the MCA blood velocity between symptomatic and asymptomatic sides of greater than twenty-five percent was considered abnormal.¹³⁸ Change in symptomatic MCA blood velocity during the first five days or until the second CT brain scan (whichever was the sooner) was defined as an increase of at least twenty-five percent in the symptomatic MCA blood velocity of the blood velocity on the asymptomatic side. Thus an increase in the symptomatic MCA blood velocity from undetectable to twenty-five percent, or from twenty-five to fifty percent, etc, or even from an apparently normal value (ie 100%) to twenty-five percent greater than that on the asymptomatic side (ie 125%) was counted as an increase. The maximum change in the symptomatic MCA blood velocity was taken as the blood velocity immediately prior to the second CT brain

scan (days "3 to 7") minus the admission value. Care was taken to distinguish between increased velocity due to stenosis (a focal area of velocity increase in the MCA main stem with damped low velocity distally) and hyperaemia (increased velocity throughout the whole detectable MCA main stem). Where a stenosis was suspected, the velocity detected in the part of the MCA immediately distal to the area with the high velocity was used to calculate the difference between the symptomatic and the asymptomatic MCA blood velocities.

Some patients also had an MCTT study done to confirm the pattern of vascular pathology as predicted by TCD. A few patients were randomised in the streptokinase trial (see Part 4) so also had a cerebral angiogram pre and post treatment infusion. Both of these techniques provided useful confirmation of the pattern of cerebral arterial occlusion as shown by TCD.

The patients' End Tidal CO_2 was measured at the time of each TCD studies using the Datex Normocap 200 as described in Part 2.2, to ensure that blood velocity changes were not simply due to altered respiration. Sequential TCD studies were done with the patient in the same position, usually supine, and as near to the same time of day as possible.

3.2.7 Consent for imaging studies

Consent for the CT brain scans and TCD studies was obtained from the patient or a close relative and the attending medical staff. Often the initial CT brain scan was requested by the attending medical staff to assist with clinical management, but the second and third were usually purely for research purposes, so consent was obtained.

3.2.8 Statistical Analysis

The results of clinical examination, CT brain scans and TCD examination were entered into a database (dBase IV Ashton Tate) on an IBM microcomputer. The time course of acute infarct swelling was examined to find the time of maximum swelling. The results were analysed for the effect of change in blood velocity during the first three to five days, and the effect of a "good" initial velocity, on a) the maximum amount of swelling shown on the CT brain scan between days three and five, and b) outcome at one and three months. The effects of the age of the patient, plasma albumin and glucose on maximum swelling were also examined. These relationships were analysed using the Statistic Package for the Social Sciences program (SPSS/PC), and odds ratio analysis, with assistance from Mr J Slattery, Statistician in the Department of Clinical Neurosciences.

Part Three

Chapter Three

Does Early Reperfusion of the Cerebral Infarct Worsen Cerebral Infarct Oedema Formation and Clinical Outcome?

Results

- 3.3.1 Study patient characteristics
- 3.3.2 Haematology and biochemistry results
- 3.3.3 Clinical outcome
- 3.3.4 Summary of imaging studies performed
- 3.3.5 Imaging results - C.T. brain scans
- 3.3.6 Imaging results - transcranial Doppler ultrasound
- 3.3.7 Severe cerebral infarct swelling - association with age of patient and biochemical factors.
- 3.3.8 Severe cerebral infarct swelling - association with extent of infarct
- 3.3.9 Severe cerebral infarct swelling - association with the symptomatic MCA blood velocity - initial value and changes in the first five days after the stroke
- 3.3.10 Clinical outcome after acute ischaemic stroke - influence of changes in symptomatic MCA blood velocity in the first five days after the stroke

3.3.1 Study patient characteristics

There were 47 patients with symptoms of an extensive MCA territory acute ischaemic stroke in whom it was possible to obtain a satisfactory TCD signal of the basal intracranial arteries through the temporal bones. These were the study subjects.

Of the 47 patients, 32 had a TACI and 15 had a "large PACI" acute ischaemic stroke. The mean age of the patients was 72 years (range 29 to 90 years). Fifteen patients gave a history of previous stroke.

The probable cause of the cerebral infarct in each patient was established by careful consideration of, and search for, all common risk factors, particularly evidence of a cardiac source of embolus or ICA stenosis or occlusion. The most likely cause of stroke is given as the probable cause recognising that definite causes are difficult to define and some patients may have more than one risk factor. Seventeen patients had a severe stenosis or occlusion of the ICA. Sixteen patients had evidence of cardiac disease as a possible cause of embolism (recent myocardial infarction, atrial fibrillation, valve disease). In fourteen patients the cause of stroke was "uncertain" including one patient who had had a laparoscopic cholecystectomy in the previous week, with no other risk factors, and may have been partly dehydrated. In a few "uncertain" cases, there was more than one possible cause of stroke, for example evidence of ICA

stenosis and recent myocardial infarction. In one patient the cerebral infarct may have occurred secondary to a profound drop in blood pressure following an acute myocardial infarction, superimposed on a tight ipsilateral ICA stenosis. In three patients considered to have cardioembolic stroke, the stroke was the presenting illness and the diagnosis of "silent" acute myocardial infarction was only made retrospectively on the basis of ECG and cardiac enzyme changes in the following week. Two other patients had sustained a definite acute myocardial infarct in the week preceding their acute ischaemic stroke. One of these had had a negative echocardiogram immediately prior to the acute ischaemic stroke, but an embolus of cardiac origin remained the most likely cause.

Most patients received no specific treatment for their acute ischaemic stroke. Ten patients were randomised in a trial of aspirin, heparin, both or neither (given for the first two weeks after stroke), and three other patients were randomised in a pilot trial of intraarterial streptokinase for the acute ischaemic stroke, described in Part Four.

3.3.2 Haematology and biochemistry results:

The plasma glucose, albumin and blood haemoglobin levels for the study group are shown in Table 3.3.1. The haemoglobin values were within the normal range, but the

haematocrit values were at the lower end of the normal range. The plasma glucose (measured within 24 hours of stroke) was above the upper limit of the normal laboratory reference range in 37/47 patients. The plasma albumin (measured within one week of stroke) was below the lower limit of the normal laboratory reference range in 8/47 patients.

3.3.3 Clinical outcome

Twelve TACI patients had died by one month, and a further two had died by three months after stroke onset. Only one PACI patient died within three months of stroke onset. By three months, ten patients had returned home. Three were still alive but had made no neurological improvement. Ten patients were in long term care, and three were in rehabilitation but making good progress intending to return home eventually. The cumulative survival by infarct type up to three months is shown in Figure 3.3.1. In the OCSF²⁵ the case fatality rate for TACI patients was 39% at one month, and for PACI it was 8%. The figures for the present study are similar, with 38% of TACI and no PACI patients dead at one month.

3.3.4 Summary of imaging studies performed

All patients had at least one CT brain scan, and TCD study. Eight patients died before the third CT brain scan could be performed, and it was not possible to CT scan twelve patients within three days of stroke (because of CT scanner breakdown or servicing, delay in admission, or unwillingness of the attending medical staff to allow the patient to be moved for a CT scan). Five patients died after the first CT brain scan before the second, and seven died after the second and before the third. Three were discharged back to their referring hospital after the second CT brain scan. Therefore not all patients had all three CT brain scans. Seven patients had three, twenty patients had two and twenty had just one CT brain scan (but twelve of these were between days three and seven). Regardless of this all patients had TCD examinations, as described in the method, daily from admission in the first week, twice in the second week and once in the third week, unless the patient died or was discharged. The cumulative CT brain scan rate is shown in Figure 3.3.2 and summarised in Table 3.3.2.

Twenty-seven patients had a diagnostic MCTT study at the time of the first TCD study and thirteen patients also had a follow up MCTT study which provided additional corroborative evidence of the pattern of cerebral arterial occlusion as shown by TCD. Of the patients who did not have an MCTT study, two died within four days of symptom onset and

underwent post mortem examination, and four had cerebral angiography. Thus there were 12/47 patients where TCD was the only method of showing the pattern of cerebral arterial occlusion.

3.3.5 Imaging results - CT brain scans

The mean time to the first CT scan from stroke onset for the whole patient group was 0.68 days (SD +/- 0.61 days), to the second CT scan was 3.9 days (SD +/- 1.4 days), and to the third CT scan was 14 days (SD +/- 4.5 days). Nine patients were CT scanned within six hours, and a further 10 patients between six and twelve hours of the stroke onset.

a) Site and extent of cerebral infarction as shown by CT brain scan :

In most patients there was a visible infarct in the symptomatic area of the brain on the first CT brain scan (days "0 to 2"). Only one TACI patient had a normal CT brain scan within the first 24 hours of symptom onset (which later became abnormal), the other 31 all having clearly visible infarcts in the MCA territory, including those scanned within the first six hours. One PACI patient still had a normal CT brain scan at three days after onset (the patient was discharged to the referring hospital so no follow up CT brain scan was obtained) but the rest of the PACI patients had a visible infarct in the symptomatic area of brain on

the first CT scan (days "0 to 2").

Most patients showed the same extent of infarct on their second or third CT brain scan as was shown on the first scan. Only three patients had a more extensive infarct on the second CT brain scan than on the first, as follows : one TACI patient scanned within 1.5 hours of stroke had a negative CT brain scan, but showed a predominantly cortical MCA territory infarct (code 4) on the second CT brain scan at four days - presumably the first CT scan was too early for the infarct to be visualised ; another TACI patient had her initial CT brain scan at 12 hours after the stroke, showing an obvious extensive infarct (code 6), which had become even more extensive (code 7) by the second CT brain scan on day four (this patient had a decrease in symptomatic MCA blood velocity suggesting a decrease in blood flow to the symptomatic area during the four days, which may have caused the ischaemia to increase. The patient died on day five and post mortem examination confirmed occlusion of the MCA from its origin distally) ; the third patient, also a TACI, had a predominantly cortical infarct visible on the initial CT brain scan at six hours (code 4), which had extended to involve the whole MCA territory on the second CT brain scan at four days (code 8). No TCD flow signal was detected in the symptomatic MCA at any time in the first four days in this patient, in keeping with MCA occlusion.

No patient had a more extensive infarct on the third CT brain scan than on the second.

b) Amount of swelling in the cerebral infarct as shown by CT brain scanning :

The time course of swelling in the cerebral infarct is shown in Figure 3.3.3. This graph includes all the CT scans performed, so if a patient had more than one CT brain scan, all are included at the appropriate time. The time of peak infarct swelling was between two and four days, as found in previous studies.^{265,266,248} Some swelling was still visible in some patients up to 18 days after the stroke. Haemorrhagic transformation of the infarct with haematoma formation was not the cause of infarct swelling in any patient as there were no large haematomas.

c) Haemorrhagic transformation of the cerebral infarct as shown by CT scanning :

Only a few patients in this series developed definite areas of haemorrhage in their cerebral infarct. Two patients had haematomas between two and five cm in diameter (one on CT scan at two days, one at five days); one patient developed a haematoma less than two cm in diameter (CT scan at 14 days); and 13 patients developed minor areas of increased density bordering the infarct which were thought to represent petechial haemorrhage. The two "two to five cm" haema-

tomas did not appear to contribute greatly to the amount of infarct swelling, as the area of infarction was large in both patients and most of the infarct swelling appeared to be due to swelling of ischaemic brain.

3.3.6 Imaging results - transcranial Doppler ultrasound

The changes in the symptomatic MCA blood velocity (expressed as a proportion of the asymptomatic MCA blood velocity) with time after the stroke are plotted separately for TACI and PACI patients, to make the graphs less cluttered, in Figures 3.3.4A (TACI) and 3.3.4B (PACI). Consecutive TCD studies in the same patient are indicated by lines connecting the points. Some patients had only one study prior to death. (As this discussion concerns only the velocity in the MCA, only the first digit of the three digit TCD code is used on the graphs).

The symptomatic MCA blood velocity increased between the admission recording and the time of the second CT brain scan (between three and seven days) in eighteen patients. Of these, twelve patients had a gradual and progressive velocity increase throughout the recordable MCA length. In the six other patients a focal, very high, velocity appeared in the symptomatic MCA main stem with a low amplitude, damped velocity signal more distally, for 24 to 48 hours, later resolving to a normal velocity. The latter would be consist-

ent with the presence of a stenosis during recanalisation of the occluded artery,¹⁵⁹ and the velocity recorded in the MCA distal to the stenosis was used to calculate the symptomatic:asymptomatic MCA velocity ratio. In five of the eighteen patients the blood velocity increased along the whole recordable length of the symptomatic MCA (65 to 35 mm depth from the temporal bone window) to a value greater than that on the asymptomatic side during the first five days after stroke, consistent with "hyperaemic" flow.^{151,152} Twenty-seven patients showed no change in symptomatic MCA blood velocity from the admission value, and in two patients there was a definite decrease in symptomatic MCA blood velocity. The maximum increase observed in symptomatic MCA blood velocity (calculated as the value immediately prior to the second CT brain scan on days three to seven, minus the admission value) was 125% (ie from zero to 25% greater than the asymptomatic MCA blood velocity), and the maximum decrease observed was minus 50% (from 50% of the asymptomatic value to zero).

The admission symptomatic MCA blood velocity was considered to be "good" (normal or at least 75% of the blood velocity on the asymptomatic side - code 5 and 6) in seventeen patients, and "poor" (less than 75% of the velocity on the asymptomatic side - codes 4 or less) in thirty patients.

The TCD results were confirmed by angiography in four patients and by post mortem in two. Thirty-five patients

also had an MCTT study. Twenty-six showed complete agreement between the TCD and MCTT findings. One MCTT study suggested a worse deficit than the TCD. In the other eight the MCTT was technically unsatisfactory due to poor cardiac output. Three of the patients who developed hyperaemia in the symptomatic MCA on TCD showed a corresponding shortening of transit time.

If an increase in the symptomatic MCA blood velocity does indicate recanalisation, then the rate in our study (15/34 of the patients still alive and in hospital at ten days) was lower than the rate described in angiographic studies of 20% at 24 hours and 80% at one week after stroke (see Figure 1.3.1).^{119,123,125} This may be because our study was biased towards patients with ICA and MCA main stem occlusions (which may recanalise less easily) and excluded patients whose clinical features suggested a lacunar syndrome, whereas angiographic studies have included peripheral MCA branch occlusions which may recanalise more easily, and some also included patients with lacunar strokes whose basal intracranial arteries were probably never occluded.^{123,125}

3.3.7 Severe cerebral infarct swelling - association with the age of the patient, plasma glucose and albumin levels

There was no association between the maximum amount of swelling in the infarct and the age of the patient ($P = 0.6$, $R^2 = 0.009$, correlation -0.09). However the study included very few patients under sixty years of age.

There was no definite association between plasma albumin ($R^2 = 0.015$, correlation coefficient 0.12 , $P = 0.5$) measured in the first week after stroke onset, or plasma glucose ($R^2 = 0.07$, correlation coefficient 0.2 , $P = 0.15$) measured in the first 24 hours after stroke onset and infarct swelling (Figure 3.3.5 A and B).

One reason for the lack of association between biochemical factors and infarct swelling was the small number of patients in the study. Another reason for lack of association between plasma glucose and infarct swelling (which may also explain some of the disagreement between previous studies³³⁹) might be that the value measured within 24 hours of stroke was quite different from the patient's plasma glucose at the time of the stroke. Stress response, lack of food, failure of diabetic patients to take hypoglycaemic agents after the stroke and before the patient reached hospital could all influence plasma glucose, changing it quite markedly from the value at the time of stroke onset. The lack of any definite association in this study should not be taken to indicate a lack of influence of blood glu-

cose levels on acute infarct swelling. It merely indicates the need for a better method of estimating blood glucose at the time of the stroke, such as measurement of haemoglobin A1.

3.3.8 Severe cerebral infarct swelling - association with size and extent of infarct

The association between extent of infarct and amount of swelling is shown in Figure 3.3.6. The maximum amount of swelling (in most cases seen on the CT brain scan between three and seven days) is plotted against the maximum extent of the infarct (maximum extent seen on any of the patients CT scans). Only 43 patients were included as two were CT scanned within six hours and died within 24 hours of stroke onset (of non-neurological causes), and a further two were not scanned between three and seven days, and the infarct swelling shown at these very early and late times was unlikely to be maximal.

There was a very clear association between infarct extent and maximum swelling. As might be expected, the more extensive the infarct the greater the amount of swelling. This association was highly significant ($P < 0.000$) with a correlation coefficient of 0.744 and R^2 of 0.55. One would expect that the greater the amount of damaged tissue, the greater the amount of oedema and necrosis.

3.3.9 Severe cerebral infarct swelling - association with the symptomatic MCA blood velocity - initial value and changes in the first five days after the stroke

The main aim of the study was to examine the effect of blood velocity changes on infarct swelling, therefore two parameters of blood flow to the infarct have been examined :

- 1) the change in the symptomatic MCA blood velocity in the first five days after the infarct, and
- 2) the initial symptomatic MCA blood velocity.

1) To examine the relationship between MCA blood velocity changes and infarct swelling the patients were divided into two groups : those in whom the symptomatic MCA blood velocity increased in the first five days or until the second CT brain scan whichever was the sooner, as defined in Part 3 Chapter 2.7 (called the "velocity increase" group) and those in whom the symptomatic MCA blood velocity did not change or decreased in the same time span ("velocity no change" group). The maximum infarct swelling was plotted for both groups and shown in Figure 3.3.7.

An improvement in the symptomatic MCA blood velocity ("velocity increase" group) was associated with a 93% reduction in the odds of severe infarct swelling (CT codes "4" to "6") compared with the group with no improvement or a decrease ("velocity no change") in the symptomatic MCA blood velocity (95% confidence interval 99% to 45% reduction, $P <$

0.05). In other words 6/17 patients with no change or a decrease in the symptomatic MCA blood velocity, and 0/11 patients with an increase in symptomatic MCA blood velocity within the first three to five days after the stroke developed "severe" infarct swelling : a 7.6 fold increase in the odds of severe infarct swelling in the "velocity no change" group (95% CI 1.2 to 46.4 fold increase, $2p = 0.03$).

2) To examine the relationship between initial symptomatic MCA blood velocity and maximum infarct swelling, the patients were divided into those with "good" blood velocity in the symptomatic MCA on admission (normal or at least 75% of the value in the asymptomatic MCA - TCD code "5" or "6"), or "bad" initial velocity (50% or less of the asymptomatic value - TCD codes "0" to "4"). A graph of the initial MCA blood velocity ("good" or "bad") and maximum cerebral infarct swelling is shown in Figure 3.3.8. A "good" initial blood velocity, ie near normal or normal, probably indicated better blood flow to the infarct than in a patient with MCA blood velocity reduced by 50% or more - "bad" flow. A "good" initial blood velocity was associated with a reduction of 92% in the odds of having massive swelling (codes "4" to "6") compared with "bad" initial velocity (95% confidence interval 99% to 70% reduction, $P < 0.05$). The numbers were small, but this does appear to be favouring a trend towards less acute infarct swelling with better initial flow to the

infarct. Following the explanations given in Parts 3 Chapter 1.2 and Part 1 Chapter 4, this could mean early recanalisation was associated with less swelling, or simply that good collateral flow (through patent MCA branches) was associated with less swelling. In both situations, the smaller amount of swelling could be because of an association with a smaller cerebral infarct.

Although the numbers were small, this result appears to favour a trend towards improved blood flow to the infarct being associated with less swelling, contradicting evidence from experimental work,^{52,327,341,344,345} but not from the small studies in stroke patients.^{187,298,299,347}

The relationship between initial admission symptomatic MCA blood velocity and maximum infarct swelling (maximum amount seen) is also shown in Figure 3.3.9. Despite the wide scatter of points there is an inverse association between the initial symptomatic MCA blood velocity and maximum infarct swelling on subsequent CT brain scans (Spearman rank correlation coefficient -0.77, 95% confidence interval -0.88 to -0.59, $P < 0.05$). The more normal the initial velocity, the less the infarct swelling that developed. Again, this might have been because a better initial MCA blood velocity (due to recanalisation or good collaterals or other reason) was associated with a smaller infarct and hence less swelling.

The change in MCA blood velocity, particularly an increase indicating better flow to the infarct, rather than

the absolute value, might be more likely to cause more in farct swelling according to experimental work. The relationship between **change** in MCA blood velocity between the admission value and the value immediately prior to the second CT brain scan (at three to seven days), and **maximum** infarct swelling for all the patients is shown in Figure 3.3.10. There was no significant association between change in MCA blood velocity and maximum infarct swelling (Spearman rank correlation coefficient -0.09 , 95% confidence interval -0.5 to 0.35). This indicated that improved flow to the infarct does not obviously worsen infarct swelling, contradicting much of the experimental work.

However the effect of the increasing flow might still be masked if only the absolute maximum infarct swelling is considered. Examination of the effect of **change** in symptomatic MCA blood velocity between the admission value and the value immediately prior to the second CT brain scan (at three to seven days) on the **change** in infarct swelling up to the second CT brain scan done between three and seven days after onset when maximum infarct swelling is expected, might indicate more directly an association between blood velocity increases and infarct swelling. To assess the change in infarct swelling the difference in swelling between the zero-to-two and the three-to-seven day CT brain scans in patients who had both scans (20 patients), and the difference in symptomatic MCA blood velocity between the TCD

studies coinciding with the two CT scans was used. Also included were some of the twelve patients who had only one CT brain scan at three-to-seven days but who had a TCD study within six hours of stroke, assuming that the change in infarct swelling equalled the day three-to-seven value, and the change in symptomatic MCA blood velocity equalled the value at the time of the three-to-seven day CT scan minus the admission value. Figure 3.3.11 shows the relationship between change in MCA blood velocity and change in infarct swelling in the first five days after stroke onset as defined above. Contrary to experimental work, an increase in MCA blood velocity was associated with significantly less infarct swelling (Spearman rank correlation coefficient -0.48 , 99% confidence interval -0.78 to -0.01 , $0.05 > P > 0.01$) than if the MCA blood velocity remained low. Therefore an improvement in blood flow to the infarct in the first three to five days after stroke onset was associated with less swelling in the infarct than was persistently poor blood flow. Therefore treatments intended to improve blood flow to the infarct in the first few days after onset may not worsen infarct swelling (as suggested by experimental studies), and may be beneficial.

3.3.10 Clinical outcome after acute ischaemic stroke - influence of changes in the symptomatic MCA blood velocity in the first five days after the stroke

The outcome at three months was related to infarct size. The more extensive the infarct, the worse the outcome ($P = 0.001$).

The influence of change in the symptomatic MCA blood velocity on clinical outcome is shown in Figure 3.3.12 with the patients divided into those whose symptomatic MCA blood velocity increased ("velocity improved") and those whose velocity did not change or deteriorated ("velocity no change") as defined above. Patients whose MCA velocity improved tended to have a better outcome than those whose MCA velocity remained unchanged or decreased : the only patients who reached home were those who had had an improvement in MCA blood velocity in the first five days after the stroke. More than 50% of those with no improvement in MCA blood velocity were dead by three months. If a "good outcome" was defined as at home or in rehabilitation expecting to return home, and a "poor outcome" was anything else, then 27/29 patients in the "velocity no change" group, and 9/18 in the "velocity increase" group had a poor outcome ; a ten fold increase in the odds of a poor outcome if the symptomatic MCA blood velocity did not improve in the first three to five days after the stroke (95% CI 2.7 to 41.6 fold increase, $2p = 0.0007$). Improvement in MCA blood velocity was

associated with a non-significant reduction in the odds of death of 66% (95% confidence interval 93% reduction to 50% excess) but a reduction in the odds of death or disability (defined as still in hospital and not improving) of 93% (95% confidence interval 99% to 30% reduction). The numbers were small but favoured a trend towards improved blood flow to the infarct in the first five days leading to improved outcome.

Summary of Chapter Three

1. Cerebral infarct swelling was maximal between three and five days after the onset of the stroke symptoms.
2. The factor which most influenced cerebral infarct swelling was the size of the infarct - the larger the infarct, the greater the amount of swelling.
3. Patients with evidence of improved flow in the symptomatic MCA on transcranial Doppler ultrasound had less severe swelling in their cerebral infarct than those with no evidence of improvement in the symptomatic MCA blood velocity.
4. Clinical outcome was better in the patients with evidence of improvement in the symptomatic MCA blood velocity in the first three to five days after the stroke than in patients with no evidence of any increase in MCA blood velocity.
5. The TCD results were verified by post mortem, angiography and the MCTT in about half of the patients.

Table 3.3.1 Haemoglobin, plasma glucose and plasma albumin levels for the study patients

Haemoglobin :	normal range :	120 to 180 g/l
	mean of study group	132
	SD	+/- 20
Haematocrit :	normal range :	40 to 54%
	mean of study group	40
	SD	+/- 4
Plasma Glucose :	normal range :	3.9 to 5 mmol/l
	mean of study group	6.96
	SD	+/- 2.8
Plasma Albumin :	normal range :	35 to 50 g/l
	mean of study group	38
	SD	+/- 4.8

Table 3.3.2 Number of CT Scans Performed in Each Time Window

Total	47
CT scan 0 - 2 days	29 (7)
CT scan 3 - 7 days	30 (12)
CT scan 8 - 14+ days	22 (2)

The numbers in brackets refer to the number of patients who had only one CT scan at the time indicated.

Patients having 3 CT brain scans : 7
Patients having 2 CT brain scans : 20
Patients having 1 CT brain scan : 20 (12 of these were between days 3 and 7)

Patients who died :
after the 1st CT brain scan, before the 2nd : 5
after the 2nd CT brain scan, before the 3rd : 7

Patients discharged :
after the 1st CT brain scan, before the 2nd : 2
after the 2nd CT brain scan, before the 3rd : 7

Permission for repeat CT brain scan refused :

by attending medical staff : 5 (2 unstable condition after myocardial infarction,
1 haematemesis,
2 too emotionally unstable)

by patient or relative : 1

other reasons : lack of CT scanner time : 5
severe movement disorder : 1
patient totally uncooperative : 1

total number of patients		47
symptomatic MCA blood velocity		
improved between :	d 0-5	18
:	d 5-20	8
symptomatic MCA blood velocity		
did not change between :	d 0-5	27
:	d 5-20	18
symptomatic MCA blood velocity		
decreased between :	d 0-5	2
:	d 5-20	6
(9 patients died and 5 were discharged prior to the third week after stroke)		
initial symptomatic MCA blood velocity "normal"		7
"hyperaemic" blood velocity in the symptomatic MCA at some time in the first week		5
focal stenosis in the symptomatic MCA at some time in the first week		6
initial symptomatic MCA blood velocity :		
"good" (code"5"- "6")		24
"bad" (code"0"- "4")		17
velocity days 0 - 3 not known		6

SURVIVAL UP TO THREE MONTHS AFTER MAJOR ACUTE ISCHAEMIC STROKE

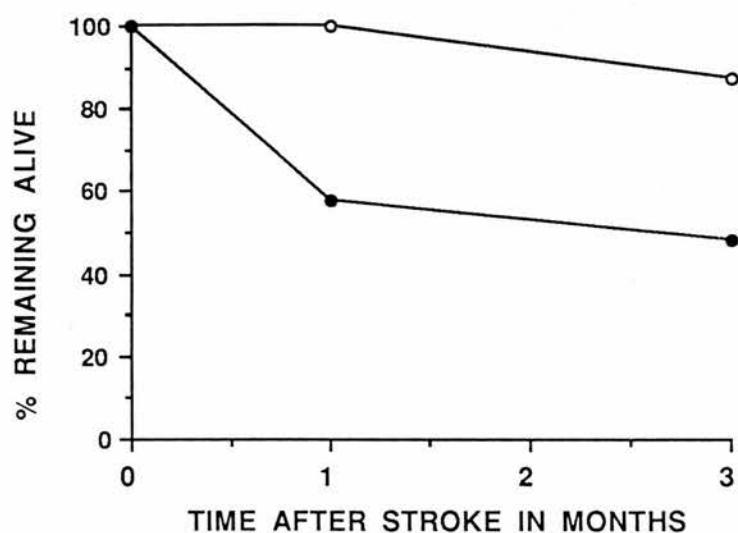


Figure 3.3.1 Cumulative survival of patients with symptoms of medium to large cortical and subcortical infarcts in the carotid territory. The 32 patients with a TACI are shown by the closed circles and the 15 patients with an extensive PACI are shown by open circles.

Cumulative CT brain scan rate in the patients with large cerebral infarcts

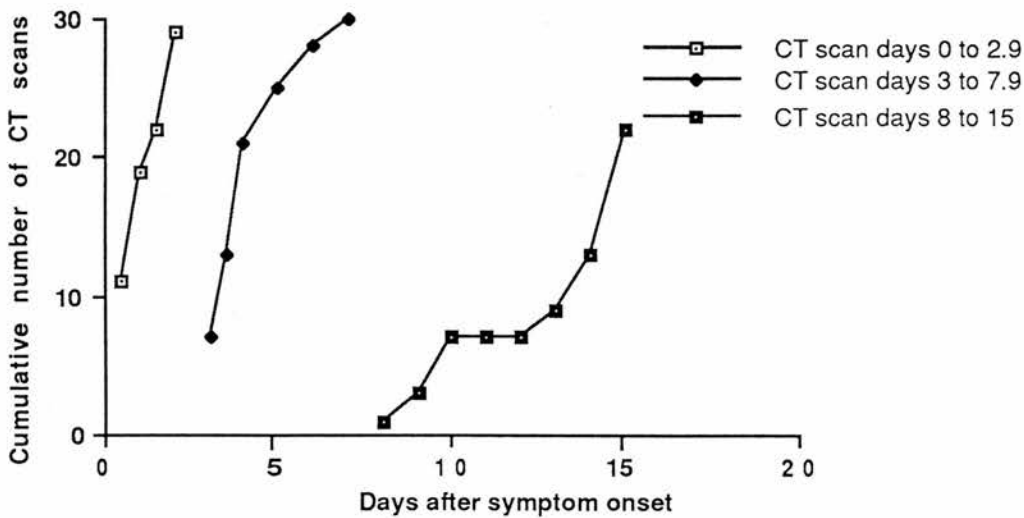


Figure 3.3.2 Number of patients having a CT brain scan in each time period : open boxes 0 to 2.9 days, diamonds 3 to 7.9 days, closed boxes 8 to 15 days after symptom onset. Five patients died after the first CT scan before the second could be performed. Seven died after the second before the third could be performed. Three patients were discharged after the second CT scan.

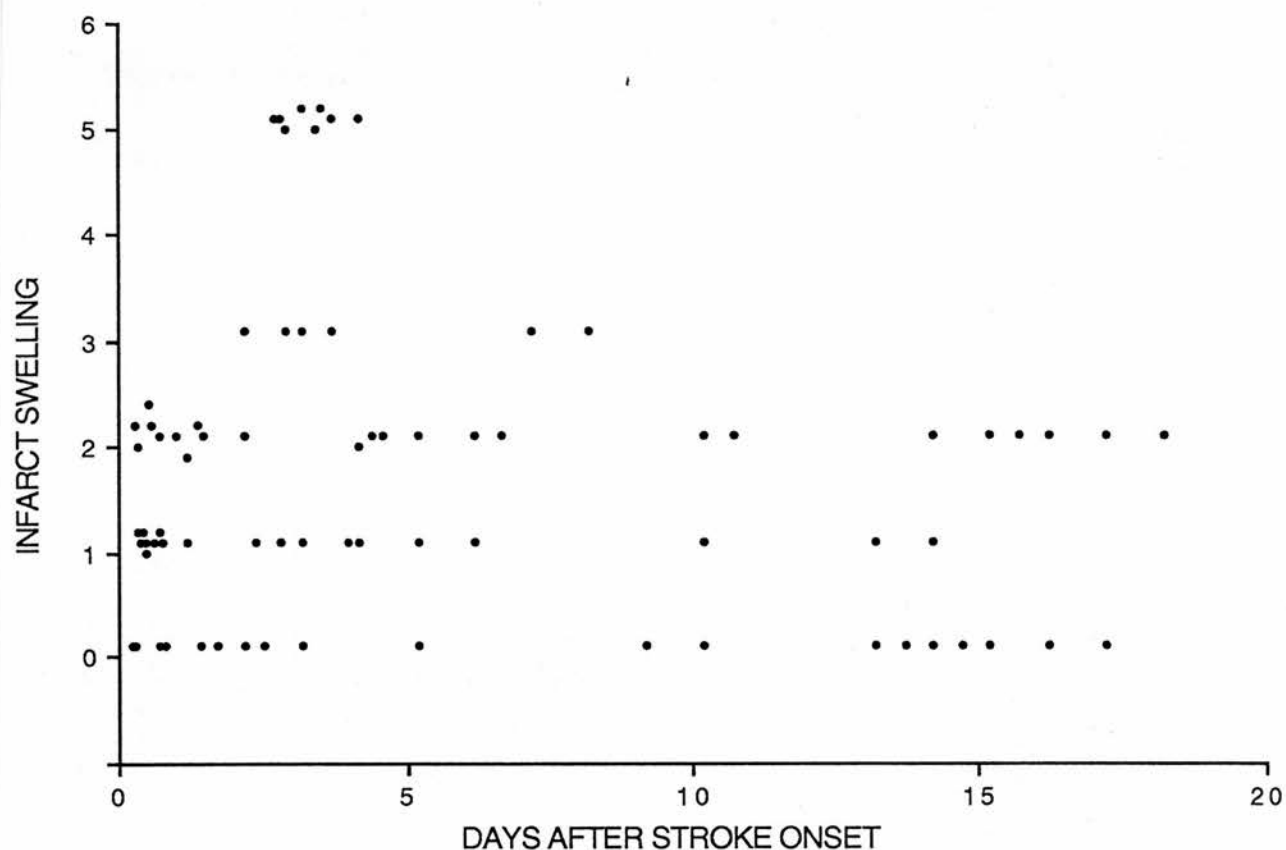


Figure 3.3.3 The time course of swelling in the cerebral infarct as shown on the CT brain scan. All CT scans on all patients are included. The code for the amount of swelling in the infarct as seen on the CT scan is indicated on the y axis. 0 = no swelling, 1 = effacement of cortical sulci overlying the infarct, 2 = 1 + mild effacement of the ipsilateral lateral ventricle, 3 = 1 + complete effacement of the ipsilateral lateral ventricle, 4 = 3 + effacement of the third ventricle, 5 = 3 + midline shift away from the side of the infarct.

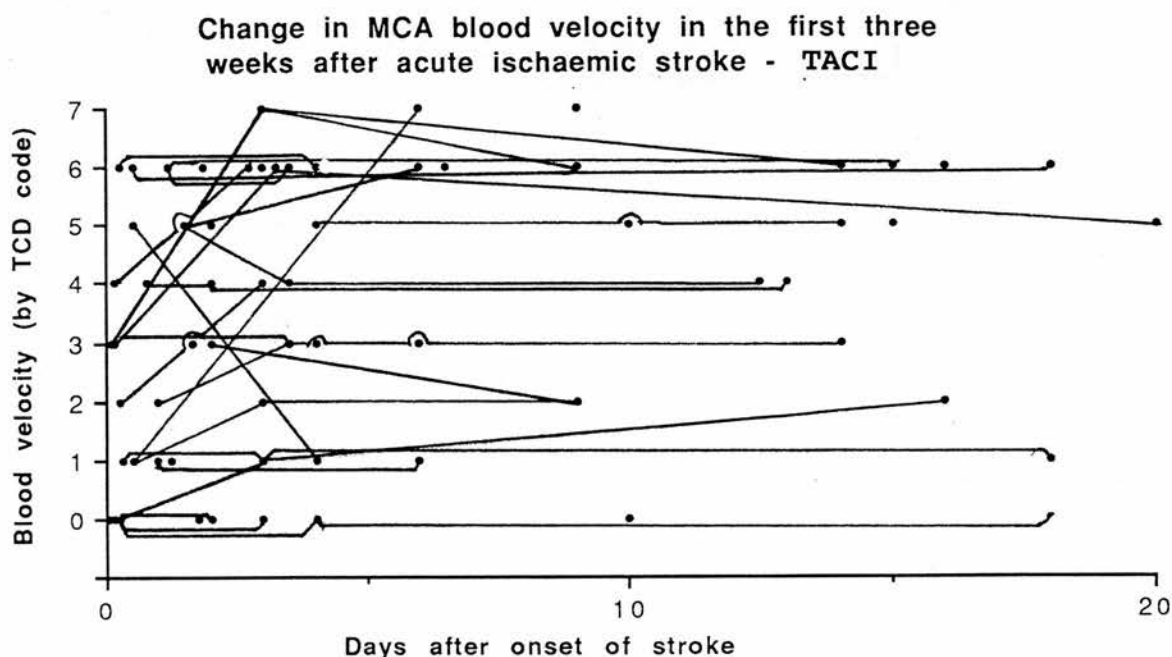


Figure 3.3.4 Symptomatic middle cerebral artery blood velocity changes in the first three weeks following a large acute ischaemic stroke - (A) patients with a TACI clinical syndrome Consecutive studies on individual patients are indicated by lines joining the dots. TCD codes (y axis) are explained in Table 2.2.3 and Appendix Four. Only the first digit of the TCD code is shown on the y axis : the code indicates the symptomatic MCA blood velocity as a proportion of the asymptomatic blood velocity, 6 being normal velocity, 5 velocity reduced to 50 to 75%, 4 a focal stenosis, 3 velocity reduced to 25 to 50%, 2 velocity reduced to less than 25%, 1 no detectable MCA velocity, 0 no MCA or ACA velocity detected, and 7 MCA velocity increased to 125% or more (ie hyperaemia).

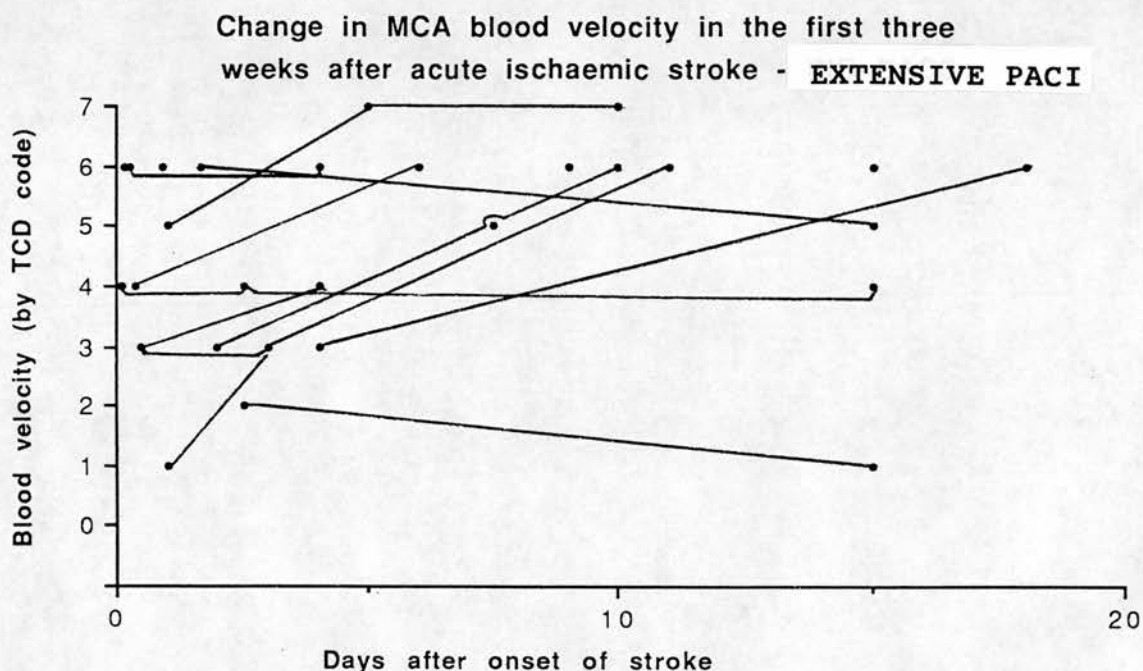


Figure 3.3.4 Symptomatic middle cerebral artery blood velocity changes in the first three weeks following a large acute ischaemic stroke - (B) patients with a PACI clinical syndrome Consecutive studies on individual patients are indicated by lines joining the dots. TCD codes (y axis) are explained in Table 2.2.3 and Appendix Four. Only the first digit of the TCD code is shown on the y axis : the code indicates the symptomatic MCA blood velocity as a proportion of the asymptomatic blood velocity, 6 being normal velocity, 5 velocity reduced to 50 to 75%, 4 a focal stenosis, 3 velocity reduced to 25 to 50%, 2 velocity reduced to less than 25%, 1 no detectable MCA velocity, 0 no MCA or ACA velocity detected, and 7 MCA velocity increased to 125% or more (ie hyperaemia).

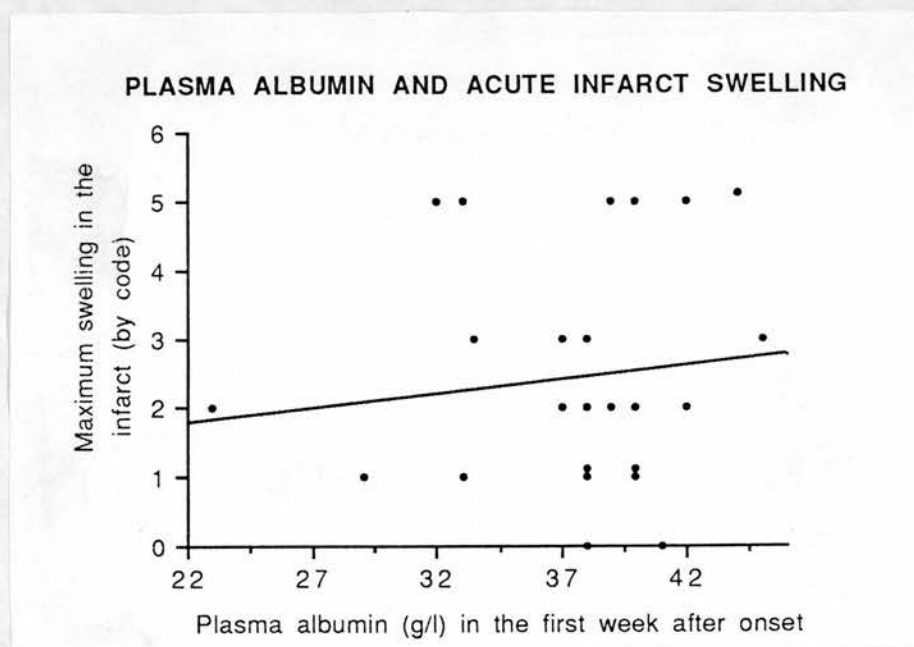


Figure 3.3.5 A: Maximum cerebral infarct swelling (on the day three to seven CT brain scan) and plasma albumin level (g/l) measured within the first week of stroke onset. The CT codes for infarct swelling (y axis) are described in Table 2.2.1 and Figure 2.2.1B. "0" indicates no swelling and "6" is massive swelling with midline shift and effacement of the basal cisterns. Slope $y = 0.96 + 0.04x$, $R^2 = 0.01$, correlation 0.12, $P = 0.54$.

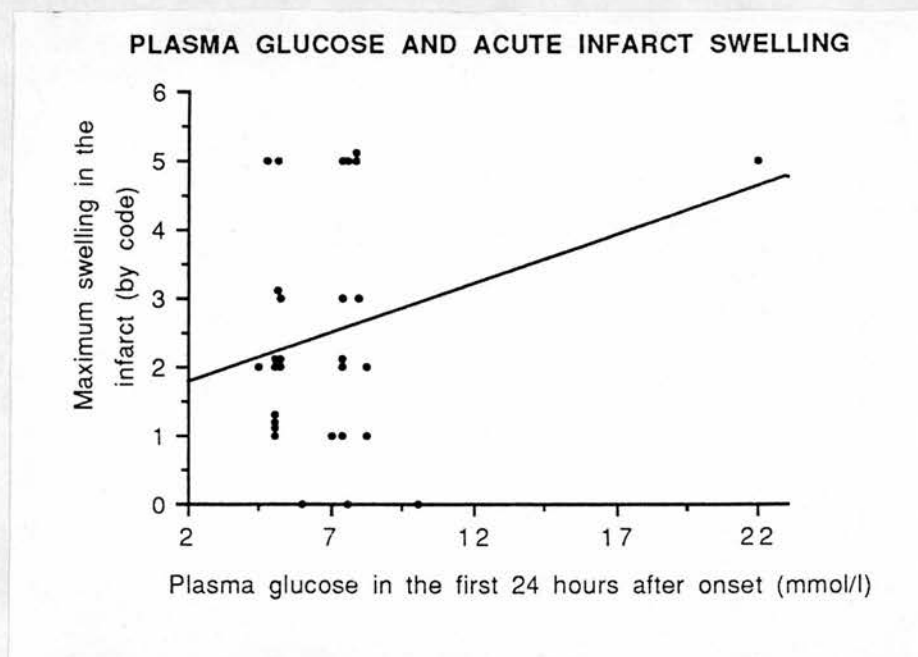


Figure 3.3.5 B: Maximum cerebral infarct swelling (on the day three to seven CT brain scan) and plasma glucose level (mmol/l) measured within the first 24 hours of stroke onset. The CT codes for infarct swelling (y axis) are described in Table 2.2.1 and Figure 2.2.1B. "0" indicates no swelling and "6" is massive swelling with midline shift and effacement of the basal cisterns. Slope $y = 1.36 + 0.15x$, $R^2 = 0.07$, correlation 0.27, $P = 0.15$.

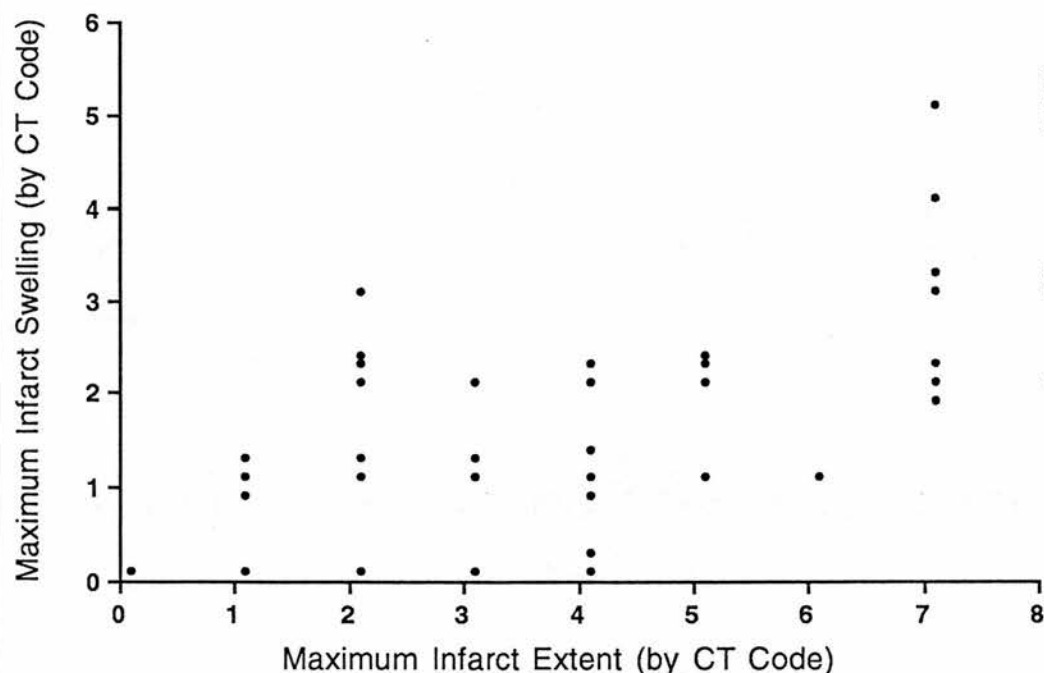


Figure 3.3.6 The relationship between the extent of the cerebral infarct and the maximum amount of swelling in the infarct. The extent of the infarct (x axis) is the maximum extent seen on any of the patient's CT brain scans ("8" is infarction of the whole MCA territory). The maximum swelling in the infarct is the maximum infarct swelling seen on any of the patient's CT scans, but usually this was on the scan at three to seven days ("6" is massive swelling with midline shift and effacement of the basal cisterns). Slope of line : $y = -0.39 + 0.55x$, correlation coefficient 0.74, $R^2 = 0.55$, $P < 0.000$). Codes for infarct extent and swelling are explained in Figure 2.2.1A and 2.2.1B, and Appendix Three. Only 43 patients are shown as two were CT scanned within six hours and died within 24 hours of stroke onset (of non-neurological causes) and a further two were scanned only before three and after seven days, and the infarct swelling shown at these very early and late times was unlikely to be maximal.

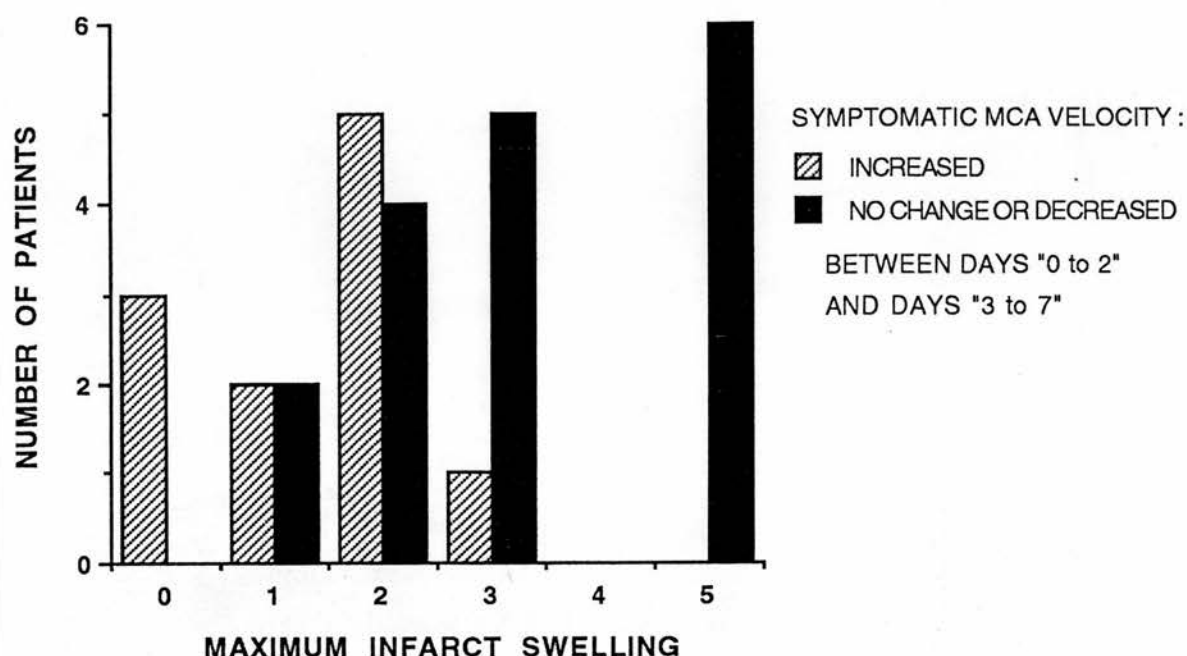
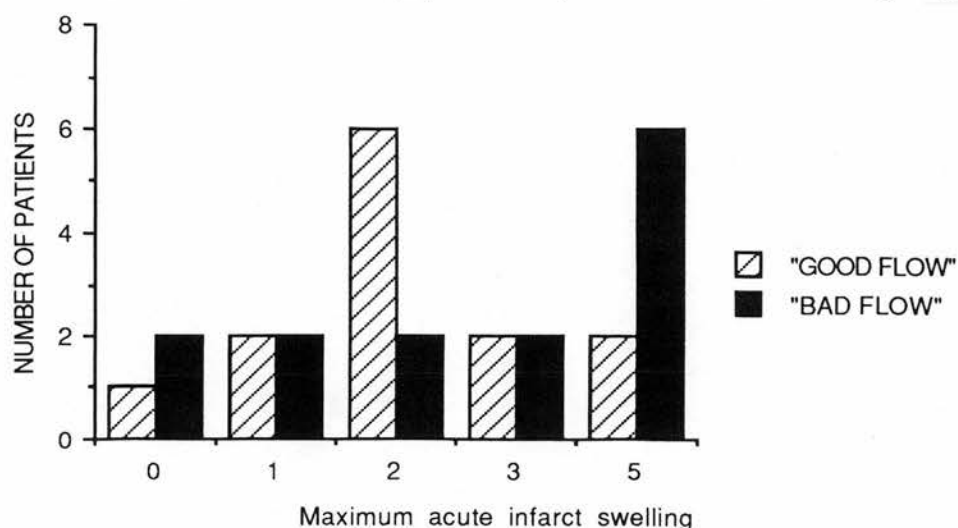


Figure 3.3.7 Maximum infarct swelling seen on the three to seven day CT scan in patients with a definite improvement in the symptomatic MCA blood velocity ("velocity increased") compared with patients with no change or a decrease in the symptomatic MCA blood velocity ("velocity no change") within the first three to five days after stroke onset. The amount of swelling is indicated by the CT code, "3" to "5" being considered severe swelling. An improvement in MCA blood velocity was associated with a 93% reduction in the odds of severe infarct swelling compared with the "velocity no change" group (95% CI 99% to 45% reduction, $P < 0.05$).

Acute cerebral infarct swelling (maximum) and initial MCA velocity : **TACI**



Acute cerebral infarct swelling (maximum) and initial MCA velocity : **EXTENSIVE PACI**

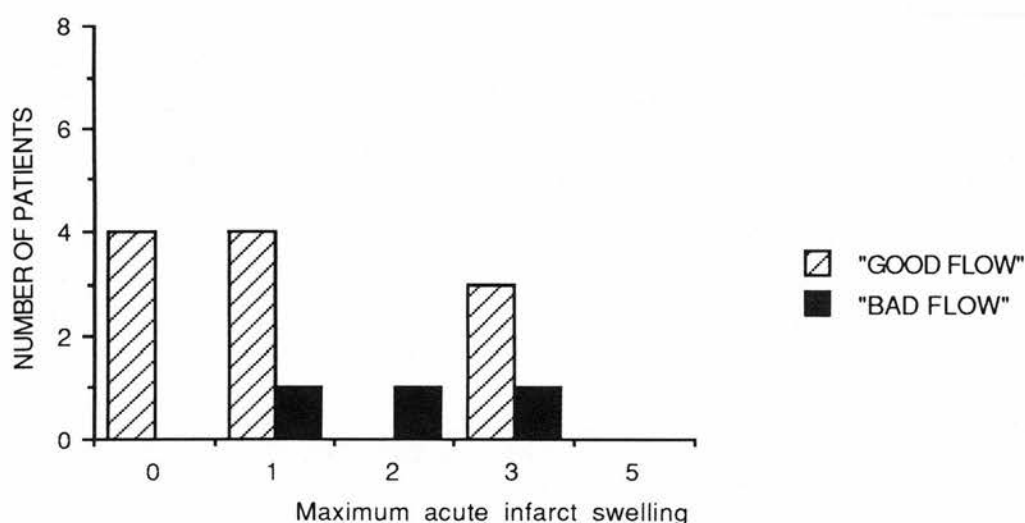


Figure 3.3.8 Maximum infarct swelling seen on the day three to seven CT scan in patients whose MCA blood velocity when first measured was "good" (ie normal or not reduced by more than 25% - TCD code "5" or "6") compared with those whose blood velocity was "poor" (ie reduced by 25% or more - TCD codes "0" to "4") A : TACI, B : PACI patients.
 The odds of having massive infarct swelling (CT codes "3" to "5") were reduced by 92% (95% CI 99% to 70% reduction) in the group whose symptomatic MCA blood velocity was "good" when compared with those whose velocity was "poor".

Initial MCA blood velocity (days 0 to 2.9) and maximum swelling
in the cerebral infarct on CT brain scan (by CT code)

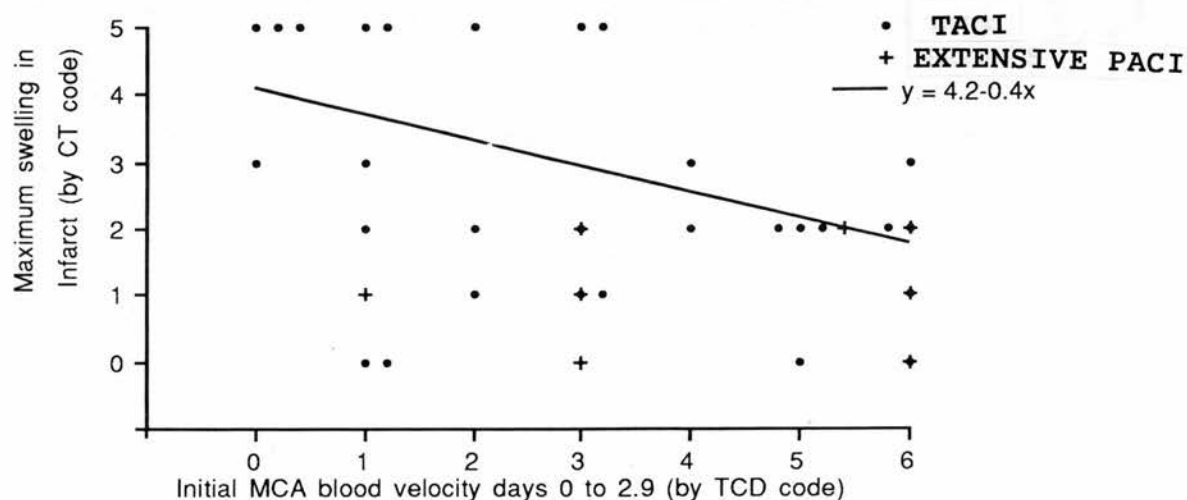


Figure 3.3.9 Symptomatic MCA blood velocity when first measured and maximum infarct swelling as seen on the CT scan at three to seven days. On the y axis "0" = no swelling and "5" = massive swelling. On the x axis "0" = MCA blood velocity undetectable, "6" = normal. Slope $y = 4.2 - 0.41x$, $R^2 = 0.3$, correlation -0.77 , 95% CI -0.88 to -0.59 , $P < 0.05$. Codes for MCA blood velocity are explained in Table 2.2.3 and Appendix Four (only first digit of code used in the plot), and for cerebral infarct swelling in Figure 2.2.1b and Appendix Three.

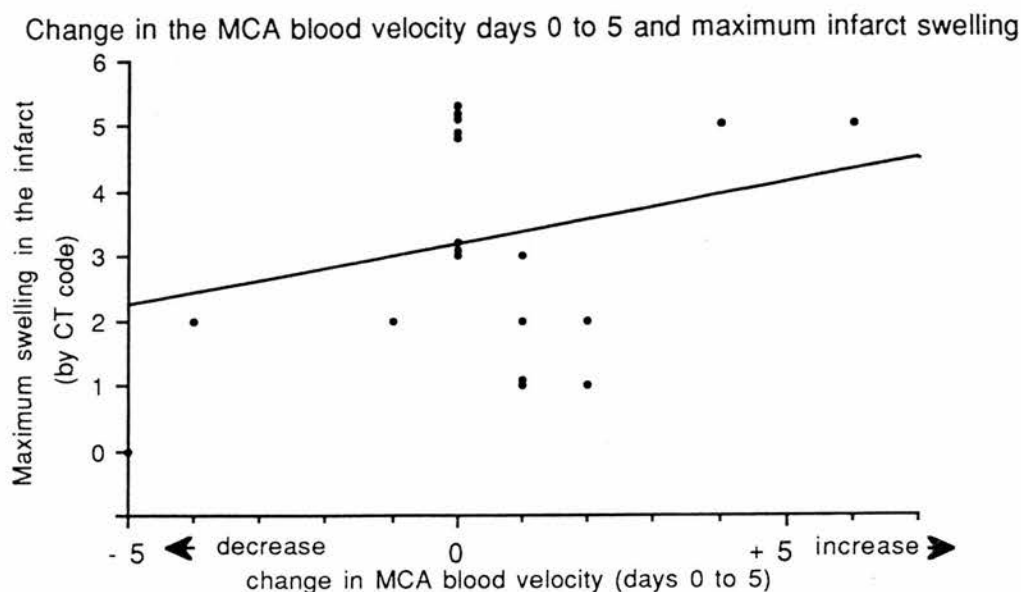


Figure 3.3.10 Change in the symptomatic MCA blood velocity within the first three to five days of stroke onset and maximum infarct swelling as seen on the CT scan at three to seven days.

"0" = no swelling and "6" = maximum swelling. The change in symptomatic MCA blood velocity is indicated as the difference between the value on admission and the value immediately prior to the day three to seven CT scan using the first digit of the TCD code (ie a "2" on admission and a "5" prior to the day three to seven CT scan would be an increase in MCA blood velocity of "+3"). The correlation coefficient was -0.09 (95% confidence interval -0.5 to 0.35, NS). Codes for infarct swelling are given in Figure 2.2.1b and Appendix Three, and for TCD blood velocity in Appendix Four.

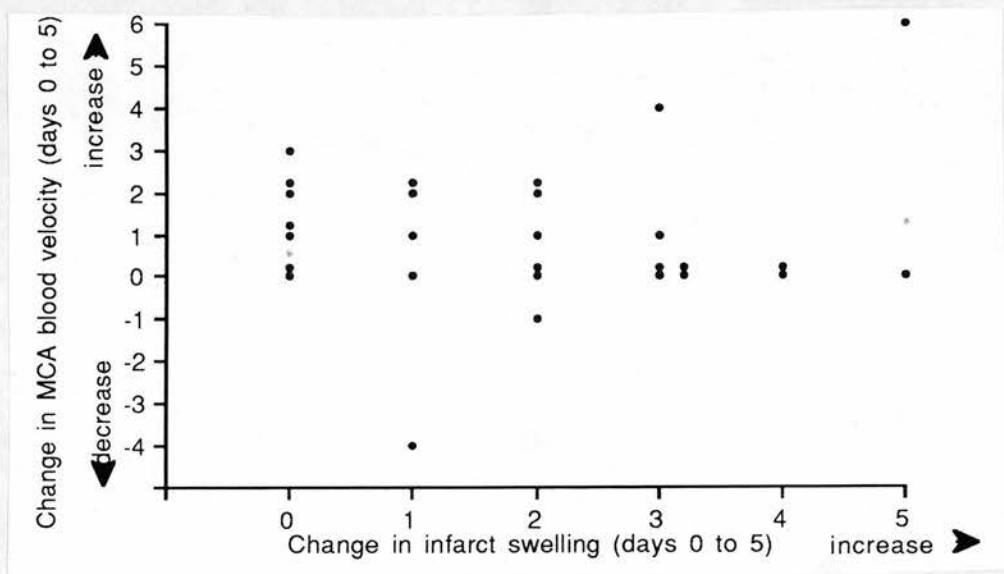


Figure 3.3.11 Change in the symptomatic MCA blood velocity in the first three to five days after the stroke and the change in infarct swelling between the day 0 to 2.9 and the day 3 to 7 CT scans in the 20 patients who had both scans. Also included are some of the twelve patients who had only one CT scan at three to seven days but who had their first TCD study within six hours of the stroke, assuming that the change in infarct swelling equalled the day three to seven value. The change in symptomatic MCA blood velocity is indicated as the difference between the value on admission and the value immediately prior to the day three to seven CT scan using the first digit of the TCD code (ie a "2" on admission and a "5" prior to the day three to seven CT scan would be an increase in MCA blood velocity of "+3"). Correlation coefficient -0.48, (95% confidence interval -0.78 to -0.01, $0.05 > P > 0.01$). Codes for infarct swelling are given in Figure 2.2.1b and Appendix Three, and for TCD blood velocity in Appendix Four.

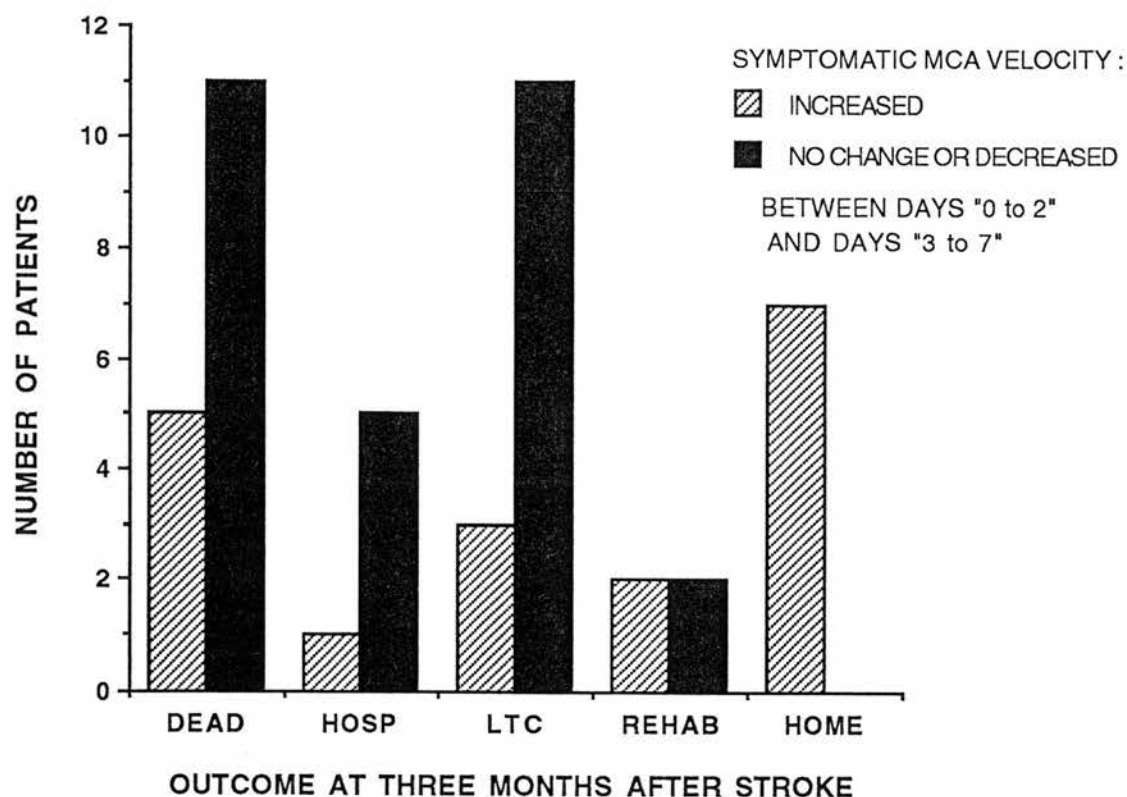


Figure 3.3.12 Outcome at three months after acute ischaemic stroke in patients whose symptomatic MCA blood velocity increased ("velocity increased") compared with those whose blood velocity did not change or decreased ("velocity no change") in the first five days after stroke onset. "LTC" = long term care, "HOSP" = still in hospital with no improvement neurologically, "REHAB" = in a rehabilitation ward with a good chance of returning home. A "good outcome" = at home or in rehabilitation expecting to return home. Thus, 27 of 29 patients in the "velocity no change" group, and 9 of 18 patients in the "velocity increased" group had a poor outcome : a 10 fold increase in the odds of a poor outcome (95% CI 2.7 to 41.6 fold increase, 2p = 0.0007).

Part Three

Chapter Four

Does Early Reperfusion of the Cerebral Infarct Worsen Cerebral Infarct Oedema Formation and Clinical Outcome?

Discussion

3.4.1 Discussion of the results

3.4.2 Summary of Part Three

3.4.1 Discussion of the results

In the simplest terms, this study has shown that improved blood flow to the ischaemic brain in the first few days after stroke was associated with lesser degrees of infarct swelling and a better clinical outcome than if the symptomatic artery had remained occluded.

The number of patients in this study was small, but it represents the largest prospective study of cerebral infarct swelling and blood flow changes following acute ischaemic stroke to date, and was the largest study of blood velocity changes and clinical outcome.

Only patients with symptoms of extensive MCA territory ischaemia were included as the MCA is the easiest and most reliable of the basal intracranial arteries to record from by TCD.^{128,129,134,139,140} The entry point to the study was symptoms indicating extensive MCA territory ischaemia, not the CT brain scan appearance, or MCA blood velocity abnormalities. If the CT brain scan appearance had been the entry point, patients with symptoms of extensive MCA territory ischaemia, but no (or only minimal CT signs) of infarction, would have been excluded, thus immediately biasing the study.

The small proportion of patients who actually had all three CT brain scans illustrated the difficulty of studying acute ischaemic stroke patients. The mortality from extensive MCA territory ischaemia is high, and five patients had

already died before the second CT brain scan could be performed. Another seven died after the second CT brain scan before the third could be performed. This, plus the inevitable loss of scanning facility because of CT scanner breakdowns and service days, meant that the CT scanning rate was lower than originally hoped for. On several occasions, it was difficult to persuade the attending medical staff to allow the patient to be moved, even though the patient could be transported on their bed to the CT scanner. The prevailing attitude towards stroke patients among the general physicians seemed to be that there was nothing to be learned from doing investigations (regarded as meddlesome), an attitude which was also responsible for the very low post mortem rate in our hospital, but also apparently in the USA.³¹⁵ This, plus the low priority given to stroke patients by ambulance and hospital staff, probably hampers acute stroke research everywhere, and a change to a more positive attitude would probably be helpful.

In this study a blood velocity increase in the MCA was interpreted as improved blood flow to the arterial territory, but there were a number of possible explanations of the mechanism of the velocity increase : 1) recanalisation of the occluded MCA main stem ; 2) persistent MCA major branch occlusion with hyperaemia in the patent branches ; 3) reperfusion of an occluded major branch without any hyperaemia ; or 4) recanalisation of multiple distal branch occlu-

sions. In each case, whether by reperfusion or hyperaemia, the blood flow to the ischaemic area was improving, though whether it was to the periphery of the infarct or to the core cannot be determined from simple velocity readings from the MCA main stem. The validity of extrapolating blood velocity changes to blood flow changes has been discussed in detail also in Parts 1.4 and 3.1.2, and within the simple criteria used, it was not unreasonable to use velocity changes to infer blood flow changes. Fluctuations in the MCA blood velocities and variation in the side-to-side symmetry occur within short time intervals in normal individuals,^{139,157} so probably also occur in pathological conditions. To try to keep blood velocity fluctuations to a minimum, the serial TCD studies were performed at the same time of day, with the patient in the same position (usually supine), with measurement of the End Tidal CO₂ to ensure that there were no major changes in respiration. In order to be counted as an increase, the symptomatic MCA blood velocity had to increase by at least 25% of the value on the asymptomatic side, which is outside the side-to-side asymmetry found in normal individuals.^{138,139,157} As the true direction of the MCA cannot be assessed with spectral TCD, and to try to reduce inaccuracies in velocity measurements occurring as a result of stretching or distortion of the MCA (from infarct swelling causing mass effect) the MCA velocity measurements were always made at the same depth, and the direction of the

probe and its position on the temporal bone noted so that any gradual change in MCA position in the course of the serial TCD studies could be assessed. In fact, this was not a problem as the MCA positions did not appear to alter in any of the patients. The patients with the most extensive infarcts tended to be those with undetectable MCA (+/- ICA) blood velocities, indicative of ICA and MCA occlusion, but possibly with detectable reversed flow in the ACA and detectable flow in the PCA. Thus, as long as only large velocity increases were used to indicate change, and as long as it was accepted that this change might indicate one of several different mechanisms as outlined above, it was probably not unreasonable to infer that an increase in the symptomatic MCA blood velocity meant increased flow in the MCA main stem to the MCA territory.¹³⁷

The TCD findings were corroborated by other means in more than half of the study patients (MCTT study, angiography or post mortem). Cerebral arterial occlusions are not static after an acute ischaemic stroke, therefore arterial blood velocity measurements will change with time after stroke onset. It is not valid to assume that the symptomatic arterial blood velocity measured five hours after the stroke is the same as the value immediately after the stroke, or the value 24 hours later. The nearer in time to the stroke onset, the more likely that the blood velocity is as it was immediately after the stroke, so any increase

measured from that point is more likely to represent "improved flow" or recanalisation. A normal blood velocity measured soon after the stroke may mean that the artery has already recanalised, or that the block is very peripheral, or that the flow in the patent branches is so good that it masks the effect of one large branch being occluded. With TCD it is simply not possible to distinguish between these possibilities. Whichever is the correct explanation, a "normal" blood velocity suggests better blood flow than a patient with a greatly reduced or "poor" blood velocity. Therefore it is important to remember that the TCD findings are dynamic after acute ischaemic stroke, and the state of the arterial circulation in the hours or days prior to the study cannot be assumed from the TCD result at one point in time.

The cerebral infarcts were visible in almost all the TACI patients scanned within 12 hours of symptom onset, and many of the PACI patients. Even patients scanned as early as two hours had clearly visible (though subtle) infarcts. The subjective impression was that infarcts involving the basal ganglia were easier to see than cortical infarcts because of the loss of visibility of the lentiform nucleus. The dissociation of infarct extent from infarct swelling was simple in practice. There were very few disagreements between the two neuroradiologists reviewing the CT brain scans, and usually this was over minor degrees of swelling (ie a "2"

instead of a "3"), not major (ie a "2" instead of a "5"). Part Two Chapter Three gives the results of the formal interobserver agreement study for site and extent, swelling, and haemorrhagic transformation of cerebral infarcts as seen on CT brain scans. Previously studies of infarct swelling in stroke patients have simply measured infarct volumes serially on CT brain scans, 227,255,265,266,305 and found that the volume increased during the first week and thereafter decreased. But this measure gave no information about why the volume was increasing - whether the infarct had become more extensive or just more swollen. Volume measurements also give no information about the extent of the infarct and the amount of swelling due to it.

In order to examine the relationship between the swelling and extent of infarction, and between infarct swelling and other factors, a method of separating the infarct swelling from extent was required. In practice, the method described in this thesis was simple to apply and clearly separated infarct swelling from extent. For each given infarct extent there were several possible amounts of swelling. For example a medium-sized infarct involving the anterior half of the peripheral part of the MCA territory (CT code "4") could have anything from no swelling (swelling code "0") to enough swelling to cause midline shift (swelling code "5"). Similarly an extensive infarct involving the whole MCA territory (code "8") could have no swelling ("0")

or maximum swelling causing midline shift and effacing the basal cisterns (swelling code "6"). Even the smallest cortical infarct (CT code "1") could have no swelling, or if the swelling was maximal, cause some effacement of the lateral ventricle (swelling code "2" or "3"). Therefore the variable amount of swelling for each infarct extent made it feasible to study the influence of factors on infarct extent and swelling.

The clinical outcome measure was even simpler than the CT brain scan and TCD measures - was the patient alive and at home at three months after the stroke, or not? Such a simple outcome measure would probably not suffice in more sophisticated studies for example in drug trials, but was adequate for this observational study.

The strongest risk factor for severe infarct swelling was the extent of the infarct - the more extensive the infarct, the greater the amount of swelling and the worse the outcome. Infarct size may have confounded all the other variables examined, particularly the MCA blood velocity changes, but the small number of patients in the study meant that it was not really possible to perform useful multiple regression analyses. However the likely effect of infarct size and extent should be kept in mind when interpreting the effect of the blood velocity changes. It was possible to compensate in part for infarct size by examining the effect of change in MCA blood velocity on change in infarct swell-

ing, although this reduced the number of patients even further because of failure to serially scan all patients.

The changes in symptomatic MCA blood velocity appeared to have the opposite effect on swelling to what might have been expected from experimental work.^{52,341,344,345} Patients whose symptomatic MCA blood velocity increased within the first five days after the stroke had less swelling than those with no change or a decrease in the MCA blood velocity. In addition, the greater the change in the velocity, the less the infarct swelling. The latter association was quite strong (Spearman rank correlation coefficient -0.48 , $0.05 > p > 0.01$) despite the small number of patients in the study. These latter two factors provide the best evidence that in stroke patients, improved blood velocity in the main artery supplying the infarct (implying reperfusion) was beneficial in causing less infarct swelling and a better clinical outcome. The improved clinical outcome was also good evidence against "delayed reperfusion injury" being clinically significant.^{58,344,345}

Was it possible that patients with early reperfusion and massive infarct swelling who died early were missed from the study? None of the patients who died within the first five days had any improvement in their symptomatic MCA blood velocity, the blood velocity remaining almost zero in all but one patient who had a near-normal blood velocity within eight hours of the stroke but which declined to zero by day

three. It seems unlikely that any patients were missed because they died too quickly to be imaged because a very complete register of all stroke patients admitted to the hospital was kept by the physicians with an interest in stroke during the time of the study.

The age of the patient had no apparent association with infarct swelling. This may be because there were too few patients under the age of 60 years in the study, or because age has no effect on infarct swelling.

There was no association between plasma glucose measured within 24 hours of onset of stroke, or plasma albumin measured within a week of stroke, and infarct swelling. As discussed in Part 3.1.3 and 3.3.7, the lack of association with plasma glucose may be because the measured value was different from the value at the time of the stroke. Most of the patients had elevated plasma glucose within the first 24 hours of stroke, possibly part of the stress response. The lack of association with plasma albumin may have been because a) there is no association between plasma albumin and infarct swelling, b) very few patients had a low albumin, or c) the small number of patients in the study.

Within these very simple criteria, it would appear that contrary to experimental evidence, an improvement in blood flow to the ischaemic/infarcted tissue was beneficial - it was associated with less swelling in the infarct (or

certainly no worse swelling) and a better chance of recovering sufficiently to return home after the stroke. No improvement in flow was associated with more infarct swelling and greatly reduced chance of going home. This is in keeping with the recently published work of Ringelstein et al²⁴³ showing that haemorrhagic transformation of the infarct was reduced, and clinical outcome improved, by reperfusion of the ischaemic tissue (demonstrated by angiography or TCD) in patients with acute carotid territory ischaemic stroke. Patients who did not reperfuse (spontaneously or therapeutically induced) had larger infarcts with more haemorrhage and worse clinical outcome. Similar results have recently been published by Moulin et al²⁶⁰ (demonstrated by angiography, TCD or SPECT) and Baird et al²⁷³ (demonstrated by SPECT) on clinical outcome in patients with or without reperfusion following thrombolysis for acute carotid territory ischaemic stroke.

The implication of these findings is that treatments intended to increase blood flow to the infarct in the first few days should be beneficial assuming that the risk of other serious adverse effects, such as haemorrhagic transformation, is small. Therefore thrombolysis is unlikely to cause severe infarct swelling simply by speeding recanalisation. Most of the velocity changes examined in this study occurred after 24 hours. It is likely that if improved blood flow to the infarct results in better clinical outcome that

most benefit will occur if reperfusion is as early as possible after stroke onset, but these results suggest that there may still be some benefit from reperfusion even after several days. Hopefully thrombolysis would be administered and cause recanalisation within 24 hours of symptom onset, and not up to three to five days. Therapeutic recanalisation, occurring earlier, might be associated with even more improvement in outcome than shown in this study, which relied in most cases on spontaneous recanalisation occurring later after stroke onset. This is therefore further supportive evidence for methodologically sound, large trials of thrombolytic and antithrombotic drugs in acute ischaemic stroke.

Summary of Chapter Four

1. 47 patients with symptoms of large MCA territory acute ischaemic stroke are described.
2. The time of maximum infarct swelling was between two and five days after stroke onset.
3. Various patterns of change in the symptomatic MCA blood velocity were observed, some improving, some passing through a "hyperaemic" phase, some a "stenotic" phase, some not improving or deteriorating. Patients with a TACI stroke had a lower initial blood velocity in the symptomatic MCA than those with a large PACI stroke.
4. Acute infarct swelling was most strongly correlated with the size and extent of the infarct.
5. The better the initial MCA blood velocity, the less the swelling and the better the outcome.
6. If the symptomatic MCA blood velocity improved within the first five days after stroke onset the clinical outcome was better than if the MCA blood velocity did not improve or deteriorated.
7. Age, plasma glucose and albumin did not obviously influence swelling in the infarct.
8. Reperfusion injury may occur, but reperfusion appeared to be associated with a better outcome than not reperfusion.
9. This result has favourable implications for trials of treatments for acute ischaemic stroke intended to increase

blood flow to the ischaemic/infarcted tissue in the first few days after the stroke such as thrombolytic or antithrombotic drugs.

This study was presented at the Second European Stroke Conference in Lausanne, Switzerland, in June 1992. The authors were awarded the prize for the best work presented orally at the conference, and in consequence the paper describing the work was automatically accepted for publication in *Cerebrovascular Diseases*. A copy of the final paper is included in Appendix 9.

Summary of Part Three

1. Experimental work on the formation of oedema in acute cerebral infarcts is described, with emphasis on the influence of changes in blood flow to the infarct at different times after stroke onset.
2. The methodology of the study to examine the effect of changes in blood flow to acute cerebral infarcts in stroke patients using non-invasive imaging techniques, and largely taking advantage of the tendency towards spontaneous recanalisation is described.
3. Patients whose blood flow to the infarct improves during the first three to five days after onset of the infarct have significantly less swelling in their infarct, and a significantly better outcome than those whose blood flow remains poor.
4. Therapies aimed at improving blood flow to cerebral infarcts in the first 24 hours after symptom onset have a good chance of being beneficial.

Part Four

Thrombolysis in Acute Ischaemic Stroke -

Does it Work?

Part Four

Chapter One

Thrombolysis in Acute Ischaemic Stroke - Does it Work? :

Introduction :

4.1.1 Introduction

4.1.2 Theoretical reasons why thrombolysis might be beneficial in acute ischaemic stroke

4.1.3 Review and overview analysis of all published data on the use of thrombolysis in acute ischaemic stroke.

4.1.1 Introduction

The possibility of using thrombolytic drugs to treat acute ischaemic stroke was the stimulus which initiated this project. In Part Four the following will be discussed :

- a) the theoretical reasons why thrombolysis might be beneficial in acute ischaemic stroke;
- b) a review and overview analysis of the results of studies on the use of thrombolytic drugs to treat patients with acute ischaemic stroke to date;
- c) describe the protocol for the pilot randomised controlled trial of intraarterial thrombolysis in patients with acute ischaemic stroke;
- d) the results of the trial thus far.

4.1.2 Theoretical reasons why thrombolysis might be beneficial in patients with acute ischaemic stroke.

So far, despite intensive research efforts, no effective treatment for acute ischaemic stroke has been found. It remains the third commonest cause of death in the developed world, preceded by ischaemic heart disease and all cancers combined.³⁴⁸ However unlike ischaemic heart disease and cancer, stroke leaves many more people disabled and dependant on family and social or health services. Despite a decline in stroke mortality in some but not all countries,³⁴⁸ there is rather little evidence of a decline in incidence.⁶³ Therefore, anticipated demographic changes,

and thus increasing stroke numbers, make it even more important to find an effective treatment.⁶⁵

Therapeutic approaches to the treatment of acute ischaemic stroke should reflect logical application of our present understanding of the sequence of events in the ischaemic brain leading to cerebral infarction. Following interruption of the blood supply, some tissue probably suffers irreparable damage within minutes, but a variable amount remains in a "shut down" but viable state possibly for several hours or even days.⁵¹ The concept of this "ischaemic penumbra" is now well established by electrophysiological work in animals⁵³ and Positron Emission Tomography (PET) in stroke patients.^{50,54,349} Neutralisation of toxic metabolites released from infarcted cells or restoration of the blood supply might save the ischaemic tissue and improve outcome. Thus two basic approaches have evolved, a) to protect ischaemic but still viable neurones from further damage by toxic metabolites, and b) to improve the blood supply to ischaemic brain.

Using the first approach, nimodipine has not been shown to be of any benefit in moderately large groups of patients.⁷¹ Newer excitatory amino acid antagonists are being evaluated but may have unacceptable toxicity (eg psychosis and cardiac arrhythmias), and it remains to be seen whether the benefit in animals can be translated into benefit in elderly stroke patients.⁷⁰

Using the second approach, haemodilution is ineffective in the generality of ischaemic stroke patients.⁶⁸ Antithrombotic therapy (with heparin, warfarin or aspirin) has not been properly tested in large randomised clinical trials. Although variably used in acute stroke,⁶⁹ we do not know if these drugs improve outcome. A large randomised controlled trial of aspirin and heparin in acute ischaemic stroke (the International Stroke Trial) has recently begun in Europe and in the USA.³¹⁴

That leaves thrombolysis, a theoretically attractive treatment with proven ability to dissolve arterial thrombus elsewhere in the body with clinical benefit,³⁵⁰ but with the potentially unattractive adverse effect of converting a simple (pale) infarct into a haematoma. Thrombolytic drugs were first used in the late 1950's for acute stroke.³⁵¹ Since then the result of treating over 2800 acute ischaemic stroke patients has been reported in the world literature. Despite this we do not know if thrombolysis works, nor what the risks of treatment are. Most of the literature consists of case reports or small series, with only six small randomised trials.^{276,352,353,354,355,356} Rather than review historically the use of thrombolytic drugs to treat cerebral ischaemia,³⁵⁷ it is the intention to examine critically and quantitatively the evidence that thrombolytic drugs might work in acute ischaemic stroke without unacceptable risks.

Given the heterogeneity of the pathogenesis and

outcome of acute ischaemic stroke, and that the magnitude of any treatment effect may be modest, both a proper control group and adequate numbers of patients are essential to ensure an unbiased and precise trial result.³⁵⁸ Many of the reported studies have methodological inadequacies that make their evaluation of thrombolysis in acute ischaemic stroke inconclusive. It is hoped that this review will demonstrate that thrombolysis has a good chance of improving outcome in acute ischaemic stroke without unacceptable risk, and that properly conducted large randomised trials (on the scale of the myocardial infarction thrombolysis trials) would be reasonable to do and likely to yield a definitive answer.

The majority of acute focal cerebral ischaemic events are due to embolism or in situ thrombosis (see Part One, Chapter One).¹²³ A small proportion are due to "boundary zone" ischaemia secondary to a hypotensive episode or internal carotid artery (ICA) occlusion. Approximately 20% are lacunar, commonly attributed to degenerative changes in small perforating arteries.²⁴ Most of the discussion in this introduction will refer to large artery territory thromboembolic stroke.

Thrombolytic drugs work in acute myocardial infarction by lysing the thrombus quickly and restoring vessel patency.³⁵⁹ The Second International Study of Infarct Survival (ISIS-2) showed that streptokinase reduced mortality after myocardial infarction by 25%.³⁶⁰ Aspirin confers

similar benefit, and the effect of both is a 50% reduction in vascular mortality at five weeks.

In the brain, (in Caucasian populations) about 20% of presumed embolic (cardiac or artery-to-artery) middle cerebral artery (MCA) occlusions recanalise spontaneously within 24 hours and about 80% do so within one week of onset,^{119,125} but these figures are no more than "best estimates". It is difficult to extract the spontaneous lysis rate of artery-to-artery embolism from the figures for cardiac embolism (often patients have both potential sources), and there is little information on recanalisation of acute internal carotid artery (ICA) occlusions in the neck. Spontaneous reperfusion following thrombotic cerebral artery occlusion (thought to be more common in Oriental people) has been little studied but appears to be less likely than recanalisation after embolic occlusion.^{361,362} Therefore, in the population with ischaemic stroke due to large vessel disease the spontaneous recanalisation rate will be at best approximately 20% at 24 hours, but may depend on where the occlusion is (ICA or MCA), what it consists of (fibrin embolus, platelet embolus or thrombus), and its age. Although these figures emphasise the lack of information regarding spontaneous recanalisation of occluded cerebral arteries, there is clear evidence that spontaneous lysis of thrombus does occur. So, the question for thrombolytic therapy is, can this spontaneous process be accelerat-

ed in time to restore useful brain function, without unacceptable risk?

4.1.3 A review and overview of all published data on the use of thrombolysis in acute ischaemic stroke

There have been over 60 reports in the world literature to date. Six were randomised trials,^{276,352-356} and four had retrospective or non-random control groups.³⁶³⁻³⁶⁶ Of the remaining, 35 or more were so called "open trials" and 20 or so were case reports. The trials were identified by a thorough literature search (using Index Medicus), by tracing references cited in thrombolysis papers, and by discussion with other researchers interested in thrombolysis from all over the world. All published randomised trials are included, as well as all non-randomised trials, and most case reports in the English, French, German, and Japanese literature. Additional unpublished information was supplied by the investigators of the larger more recent trials. It is probable that some acute stroke patients have been treated with thrombolysis but not reported in the literature, and potential bias because of this must be borne in mind when interpreting the following analysis.³⁶⁷

Randomised trials (Table 4.1.1 and Figure 4.1.1).

Of the six randomised trials, the two by Meyer et al

352,353 were conducted prior to the invention of CT scanning so some patients with primary intracerebral haemorrhage or haemorrhagic infarction may inadvertently have been included, and thrombolytic treatment would probably have made matters worse. The numbers were small, and the outcome measure was clinical evaluation at ten days, which may be too early for valid assessment. In the first study there was no difference in outcome between the treated and control groups. In the second, larger study, the treated group fared worse. However patients were included up to 72 hours after onset, and although the mean time to treatment was not stated, trial intervention may have been too late. It is generally thought that treatment for acute ischaemic stroke should begin as soon as possible, certainly within 24 hours of onset.

The randomised trials by Mori et al,²⁷⁶ Ohtomo et al,³⁵⁴ Abe et al,³⁵⁵ and the Japanese Thrombolysis Study Group (JTSG)³⁵⁶ used CT scanning to exclude intracerebral haemorrhage as a cause of stroke before randomisation, and for follow up after treatment. Mori et al studied MCA and ICA recanalisation and found that 9/19 patients given intravenous (IV) tissue Plasminogen Activator (tPA), within six hours of symptom onset, recanalised compared with 3/12 given placebo.²⁷⁶ Ohtomo et al published a Japanese multicenter randomised trial of low dose IV urokinase (UK) in acute thrombotic cerebral infarction given within five days

of symptom onset.³⁵⁴ Abe et al (also Japanese) published a randomised trial of IV urokinase for acute ischaemic stroke given up to 30 days after symptom onset (more than half of the patients were treated four days after onset or more).³⁵⁵ The JTSG studied clinical improvement after embolic stroke and found that 37/51 patients randomised to 34 mg t-PA iv improved compared with 26/47 given placebo within six hours of symptom onset.³⁵⁶ Additional information on drug, dosage, route of administration, time to treatment and outcome measure is given in Table 4.1.1. Note that Table 4.1.1 includes not only the six truly randomised trials (upper half) but also the four nonrandomised trials (described below), which are often referred to as "controlled" trials in the literature, to emphasise the distinction.

Figure 4.1.1 shows the results of an overview analysis³⁶⁸ of death (a) and death or deterioration (b) following thrombolytic therapy for acute ischaemic stroke. The analysis is of published results for the six randomised trials, and additional information was supplied by E Mori and T Yamaguchi (for the JTSG). Although deterioration was assessed differently in each trial, the overview technique minimises the problem of trying to compare different trials and end point measurements by not comparing randomised controlled trials directly with each other. Rather, the overview compares the magnitude and direction of any treatment effect contained within the individual trials and

yields an estimate of the overall treatment effect.

Analysis of all six trials shows that the risk of death is increased by 20% with thrombolysis but with a wide confidence interval which includes the possibility of a 31% reduction to 151% excess. The risk of death or deterioration (all six trials) is reduced by 37% with thrombolysis, but the wide confidence interval includes the possibility of a 66% reduction to 14% excess.

Analysis of the four trials conducted with the benefit of CT scanning (therefore reliably excluding cerebral haemorrhage as the cause of symptoms) shows a reduction in the risk of death of 37% (95% CI : 74% reduction to 47% excess) with thrombolytic treatment, and shows a reduction in the risk of death or deterioration of 56% (95% CI : 20 to 76% reduction [$2p = 0.007$]). This provides some evidence that thrombolysis is beneficial in acute ischaemic stroke, not enough to recommend routine treatment but certainly enough to encourage larger randomised trials.

Studies with a retrospective or non-random control group (Table 4.1.1).

The study by Hacke et al³⁶³ on vertebrobasilar occlusion illustrates the difficulty of including a retrospective control group. Although the treated and control groups were similar in many respects, 12/23 (54%) of the controls were

unconscious at diagnosis and entry into the trial, compared with 15/45 (35%) of the treated group, perhaps reflecting increasing awareness of the condition and earlier diagnosis. Epidemiological studies have shown that vertebrobasilar stroke can cause mild symptoms and does not always progress to coma with the uniformly bleak outcome that Hacke et al have suggested.²⁵ Therefore, the prospective treated and retrospective control patients may have been different in prognosis, and it is not valid to use the sicker group treated conventionally as a control for the later "treated" group. The other three studies which included a "control" group, did not state how the patients were chosen or how treatment was allocated.³⁶⁴⁻³⁶⁶

"Open" trials and case reports (Tables 4.1.2 and 4.1.3).

The primary aim of these studies was to assess safety and find an optimal dose. They are a heterogeneous group of reports, some using the IV, some the intraarterial (IA) route of drug administration, different drugs, dose of drug, inclusion criteria and outcome events (recanalisation or clinical improvement). It is not possible to make any comment about benefit because there were no controls. It is even difficult to draw any conclusions about safety as the natural history of cerebral infarction is so variable and there were no controls with which the development of cerebral oedema and haemorrhagic transformation could be com-

pared.

The studies which examined reperfusion (using serial angiography) considered together showed some degree of recanalisation in 61% of patients within 24 hours. This is better than the reported spontaneous rate of 20% at 24 hours after onset (see above) and is of the same order of magnitude as was found in the acute myocardial infarction thrombolysis studies which used angiography to assess recanalisation.³⁶⁹

These conclusions are encouraging but tentative. The numbers of patients are small and there may have been publication bias,³⁶⁷ although in the field of thrombolysis in acute ischaemic stroke, positive as well as negative results seem to be presented with equal enthusiasm!

Does thrombolysis increase the risk of cerebral haemorrhage?
(Tables 4.1.4 and 4.1.5 and Figure 4.1.2)

Thrombolytic drugs given for extracranial vascular disease increase the risk of haemorrhage both in the brain and elsewhere in the body.³⁶⁰ Therefore, thrombolysis for acute ischaemic stroke might increase the risk of cerebral haemorrhage, but how big is this risk? Thrombolysis might, by reducing infarct size or other mechanism, actually reduce the rate of haemorrhagic transformation of the cerebral infarct.²⁵⁵ Studies of the natural history of ischaemic stroke suggest that approximately 5% of simple (pale) in-

farcts undergo symptomatic haemorrhagic transformation with formation of space occupying haematomas,²⁶⁷ though there is little good information on the "natural" rate of haemorrhagic transformation. Most reports are limited by the method of patient selection, for example, post mortem series, retrospective CT studies, and some prospective CT studies in which only patients who survived or deteriorated were scanned. In addition most studies include some patients who received antithrombotic treatment of some sort, and thus for several reasons may have overestimated the frequency of haemorrhagic transformation. Pathological studies show some degree of petechial haemorrhage in almost all infarcts, though CT scanning detects this less frequently^{255,275} Petechial haemorrhage is thought to be asymptomatic and thus probably does not matter clinically, although this has not been studied. Based on the best information available, we estimate that the spontaneous rate of symptomatic haemorrhagic transformation of the infarct is approximately 5%²⁵⁴ and that the rate of asymptomatic (petechial) haemorrhagic transformation is between 15% and 45%²⁷⁵ but this may be an overestimate. The rate probably varies with the extent of the infarct²⁵⁵ and possibly with stroke aetiology.²⁷⁵

Using all the published data available, the rate of haemorrhagic transformation after thrombolysis for acute ischaemic stroke was estimated. Table 4.1.4 shows the risk of asymptomatic petechial haemorrhagic transformation

(without clinical deterioration), and table 4.1.5 the risk of symptomatic intracerebral haematoma (with clinical deterioration). The true rate of haemorrhagic transformation can only be found from large randomised controlled trials (including at least several thousand patients) but summing all the data available at present may at least give an estimate of the likely order of magnitude of haemorrhagic transformation. All the data including case reports has been included so as to give as unbiased assessment as can be obtained at present. Note that the time to treatment, route of administration, type of drug and total dose of thrombolytic drug (in some studies very low doses of thrombolytic drug were used), definition of symptomatic and asymptomatic haemorrhagic transformation, and patient characteristics were different in each study. Therefore this analysis can only provide an estimate of the likely haemorrhagic transformation rate. Note the huge variation in the reported rate of asymptomatic petechial haemorrhage. This may partly reflect bias in interpretation of CT scans, or it may be due to different frequencies and timing of CT scanning after thrombolysis, different doses of drug, or inclusion of different types of ischaemic stroke and thus should be viewed with this in mind. The estimated rate of symptomatic intracerebral haematoma formation following thrombolysis (5%) is similar to the estimated expected natural history. The haematoma rate varies between studies and appears to be

higher with tPA (Figure 4.1.2), as might be expected from the recently presented ISIS-3³⁷⁰ and GISSI-2³⁷¹ results in acute myocardial infarction.

The randomised trials (with CT scanning) all found massive haemorrhagic infarction slightly more often in placebo than thrombolysis-treated patients. Mori et al²⁷⁶ found haemorrhagic transformation of mild degree in 26% of tPA treated and 33% of placebo treated patients. Ohtomo et al³⁵⁴ found 2/169 UK treated patients developed haemorrhagic transformation of their infarct of mild degree, and 1/181 placebo treated patient developed a severe symptomatic intracerebral haematoma. Abe et al³⁵⁵ found no symptomatic intracerebral haematomas with UK. In the JTSG trial there were four massive haemorrhagic infarcts in the tPA treated group and five in the control group with equal numbers of patients in each group.

None of the large "open" stroke trials found a relationship between dose of drug and symptomatic intracerebral haematoma formation, but they suggested that a time delay of over six hours from onset, hypertension, and possibly treating patients who already had a low density area visible on CT, may be risk factors.^{278,372,373} Matsumoto et al³⁷⁴ have treated 52 acute ischaemic stroke patients with a wide range of doses of UK and not demonstrated any definite relationship between cerebral haemorrhage and dose, time after onset, or age of patient but they suggested that haemor-

rhages were more often symptomatic in recanalised patients (Figure 4.1.3). No definite association with recanalisation was found in the Acute Stroke Study Group trial,²⁷⁸ nor by Miyakawa.³⁷⁵ Therefore, it appears that although one would expect thrombolytic treatment to increase the frequency of symptomatic cerebral haematoma formation, no definite association has been found in over 2800 patients that have been treated so far.

Does thrombolysis increase the risk of space-occupying oedema formation in the cerebral infarct? (Table 4.1.6)

The cause of severe infarct oedema is unclear. The aetiology of cerebral infarct oedema and its relationship to infarct perfusion has been discussed in Part Three Chapter One. The frequency of cerebral oedema with brain herniation is difficult to extract from the thrombolysis studies but does not appear to be increased. Mori et al²⁷⁶ found massive brain swelling occurred in 9% of patients who reperfused compared with 35% whose symptomatic cerebral artery remained occluded (26% of tPA and 25% of placebo treated patients).

Which drug should be used?

Most of the available thrombolytics have been tested in stroke, using the oral, IV, and IA routes of administration, and at a wide range of doses. Table 4.1.2 shows that in the small non-randomised studies so far there is little

difference in immediate patency rates between the more expensive tPA and SK or UK, and no obvious optimum dose. But, the number of patients is small and there may be publication bias. Several "open" studies have failed to identify an optimum dose.^{278,372-374}

The lack of a clear benefit for one drug or dose is not unexpected. ISIS-3³⁷⁰ and GISSI-2³⁷¹ combined had to randomise over 60000 patients to show that the reduction in vascular deaths after MI was the same whether SK, tPA or anistreplase was used. But there was a highly significant excess of cerebral haemorrhages with tPA: 7/1000 compared with 3/1000 with SK.³⁷⁶

Extrapolation from ISIS 3 and GISSI-2 suggests that the clinical benefit for thrombolysis in acute ischaemic stroke should be about the same no matter which agent is used, but the cerebral haemorrhage rate might be higher following tPA. This seems to be the case if this simple analysis of the available studies is correct (Tables 4.1.4 and 4.1.5 and Figure 4.1.2). In view of the overwhelming evidence from the 60000 patients randomised in the acute myocardial infarction trials, it would probably be preferable to study SK rather than tPA in acute ischaemic stroke, at least to start with.

What about dose and mode of administration of thrombolysis, elderly patients, and time limit to treatment after onset?

Any treatment for acute stroke must be easy to administer to avoid delay. The standard IV dose for myocardial infarction is 1.5 MU streptokinase (SK) or 100mg tPA.³⁷⁷ Smaller intracoronary doses were used in early studies to try to maximise local thrombolytic effect and reduce systemic adverse effects, but any benefit was more than offset by the extra one or two hours delay due to angiography.³⁵⁹ It is suspected that, if thrombolysis is shown to work in acute ischaemic stroke, the drug of choice will be SK 1.5 MU IV : cheap, easy to administer, least risky, and with a proven track record in acute myocardial infarction.

If thrombolysis is to be a worthwhile treatment for acute ischaemic stroke, then it should be available for the elderly, the most commonly affected age group. Cerebral amyloid angiopathy has been cited as a reason for increased risk of haemorrhage in the elderly.³⁷⁸ The few studies where thrombolytics have been used in elderly stroke patients (70 years plus) and the results for the elderly patients can be separated from the rest of the patients, do not show a definitely increased haemorrhage rate compared with younger patients (Figure 4.1.3). The Acute Stroke Study Group²⁷⁸ did not find an increased cerebral haemorrhage rate in patients up to 80 years of age. Several other reports^{379,380,381} of thrombolysis in elderly stroke patients have shown benefit

but this is anecdotal.

ISIS-2³⁶⁰ showed that in elderly myocardial infarct patients treated with thrombolysis, the proportional reduction in mortality was the same as for younger patients and the absolute reduction was greater. The elderly perhaps have the most to gain from a treatment which reduces disability from stroke, and thrombolysis certainly deserves a trial at all ages.

A time limit of six hours from onset to treatment was set by most of the recent thrombolysis studies, although the sparse data available do not show a sharp increase in adverse effects between six and 24 hours.³⁷⁴ Several Japanese studies have included patients for several days after the stroke with no obvious increase in adverse effects.^{354,355,382,383,384} Although it is unlikely that neurones will survive many hours of ischaemia, we do not really know enough about the duration of neuronal viability after acute cerebral artery occlusion to introduce time limits to treatment. Time limits can only be established by large randomised, controlled trials. In most parts of the world stroke patients go to hospital (if at all) in a "slow ambulance", and few reach hospital and have a CT scan by six hours. Although it was possible to recruit patients within 90 minutes of symptom onset in the National Institutes of Health (NIH) t-PA study^{385,386} (and very early recruitment is continuing in the NIH randomised controlled trial of t-

PA) elsewhere in the world it is likely to take many years to change the current slow referral pattern. Therefore future trials should examine the problem of maximum time limit by including patients up to 24 hours after onset; otherwise we will never know the risk/benefit ratio of thrombolytic treatment between 6 and 24 hours.

If very early treatment is the aim, is there a danger of exposing patients who are having a TIA to thrombolysis? Levy³⁸⁷ found that 50% of TIAs last less than 30 minutes, and in patients with a deficit persisting at 60 minutes, less than 2% will resolve spontaneously in each subsequent one hour period. Therefore, there is very little danger of treating a TIA with thrombolytics if patients showing distinct signs of improvement in the first one to two hours are excluded.

4.1.4 Concluding Comments

Experience with thrombolysis in acute ischaemic stroke suggests that the risks are not excessive and there may be some benefit. However, the standard of methodology used in most of the "trials" so far means that this conclusion must be very tentative and no more than hypothesis generating. It has been enough, however, to encourage Italian, Australian and American investigators who have recently started randomised trials of intravenous thromboly-

sis (SK/aspirin/both or neither, SK/aspirin/placebo, and t-PA/placebo respectively) in acute ischaemic stroke.

Considerable expertise has now accrued showing the value of thrombolysis and aspirin in acute myocardial infarction. As well as demonstrating benefit in young otherwise healthy myocardial infarction patients, ISIS-3 has shown that other subgroups of myocardial infarction patients, traditionally regarded as "high risk" for thrombolysis, gain considerable benefit from it - this includes the elderly, and those with hypertension, previous peptic ulcer, and recent stroke.³⁷⁰

It is this mass of evidence from the use of thrombolysis in myocardial infarction, as well as the limited experience in ischaemic stroke, which makes it imperative and urgent to test thrombolysis properly in acute ischaemic stroke. There is no place for more non-randomised trials in this assessment. Safety cannot be assessed unless the major adverse effects of the treatment under trial are controlled for, which in this case mimic the natural history of the disease - cerebral haemorrhage and severe infarct oedema.

Acute stroke treatment research is rejecting compounds thought to have therapeutic promise as fast as they can be invented, but with remarkably little good evidence to do so. Thrombolysis in acute myocardial infarction was almost rejected in error after innumerable small trials had missed its real benefit. It was only after the overview of

these trials³⁵⁹ and the subsequent very large trials^{360,370,371} that the clear benefit was demonstrated, clear enough to change clinical practice.³⁸⁸

Thrombolysis for acute ischaemic stroke deserves large and methodologically sound trials designed to answer a simple question : does it work ?

Fortunately, since this project began, several large and more methodologically sound trials (mentioned above in Italy, Australia and the USA) have started, and hopefully we will have a definitive answer on the benefit of thrombolysis in the not-too-distant future.

Author	Drug	Route	Dose	Time from onset	Outcome Measure	Results			
						Treated No.	%	Control No.	%
Randomised									
Meyer (352)	Fib/ Plas	iv	2.5-11.5 x 10 ⁵ u	<72hr	clinical improvement at 10 days	20	45	20	45
Meyer (353)	SK	iv	2.5-17.5 x 10 ⁵ u	<72hr	clinical improvement at 10 days	37	43	36	58
Mori (276)	tPA	iv	34-50 mg	<6hr	recanalisation	19	47	12	25
Ohtomo (354)	UK	iv	6x10 ⁴ u per day for 7 days	<5days	clinical improvement at 4 weeks	169	56	181	42
Abe (355)	UK	iv	6 x 10 ⁴ u per day for 7 days	<30days	clinical improvement at 1 and 4 weeks	54	63	53	43
JTSG (356)	tPA	iv	34mg	<6hrs	clinical improvement at 4 weeks	51	72	47	55
Non Randomised									
Hacke (363)	SK/ UK	ia	4 x 10 ⁵ u approx.	<24 hr	clinical improvement	45	44	23	0
Okada (364)	tPA	iv	26-50mg	<6 hr	clinical improvement at one month	15	47	11	9
Abe (365)	UK	iv	6-12 x 10 ⁵ u	up to 6 months	clinical improvement at one month	62	71	22	36
Larcan (366)	UK	iv	16.5-38.5 x10 ⁵ u	36hr+	clinical improvement	36	47	41	17

Table 4.1.1 "Controlled" Trials of thrombolysis for acute ischaemic stroke.

No. = total number of patients; % = % of patients who improved clinically or recanalised. (276) Where two assessment times are given, the % improved refers to the later time. JTSG = Japanese Thrombolysis Study Group (356); Fib = fibrinolytic, Pla = plasmin.

"Open" Studies of Thrombolysis for Acute Ischaemic Stroke : Recanalisation

Author	Year	Drug	Route	Dose	Number of patients	% recanalised
Del Zoppo (399)	1988	SK	IA	0.06-2.5x 10 ⁵ u	20	75
Theron (381)	1989	SK	IA	0.25-1.5x 10 ⁵ u	12	100
Maisa (400)	1988	SK	IA	2.5x10 ⁵ u	16	100
Zeumer(401)	1985	SK/UK	IA	various	29	86
Berg-Dammer(397)	1991	SK	IA	10 ⁵ u	3	100
Baird (347)	1992	SK	IV	1.5x10 ⁵ u	5	38
TOTAL FOR SK = 75 / 93 = 80 % RECANALISED						
Zeumer (394)	1984	UK	IA	0.5-1.25x10 ⁵ u	2	10
Mori (277)	1990	UK	IA	1.8-3.2x10 ⁵ u	48	44
Lehman (395)	1989	UK	IA	2-3x10 ⁵ u	10	80
Ikeda (396)	1990	UK	IA	4.2x10 ⁵ u	13	85
Siepmann (379)	1991	UK	IA	up to 7.5x10 ⁵ u	11	64
Casto (427)	1992	UK	IA	5.6x10 ⁵ u	4	80
Berg-Dammer(397)	1991	UK	IA	2-7.5x 10 ⁵ u	7	100
Mobius(398)	1991	UK	IA	3-9.5x10 ⁵ u	18	77
Seikman(380)	1991	UK	IA	8x10 ⁵ u	2	100
Matsumoto(374)	1991	UK	IA	2.4-12x 10 ⁵ u	52	58
Miyakawa(375)	1984	UK	IV/IA	7-9x10 ⁵ u	49	59
Williams (423)	1992	UK	IA	5-10x10 ⁵ u	2	66
TOTAL FOR UK = 134 / 217 = 62% RECANALISED						
ASSG(273)	1991	tPA	IV	12.5-44mg	93	36
Karnik (424)	1992	tPA	IA	20mg	1	100
Yamaguchi(403)	1991	tPA	IV	10, 20, 30 mg	58	43
Hennerici(373)	1991	tPA	IV	70mg	18	44
von Kummer(404)	1991	tPA	IV	70/100mg	27	56
Brucker (425)	1992	tPA	IV	100mg	25	89
von Kummer (426)	1992	tPA	IV	100mg	32	53
TOTAL FOR tPA = 154 / 284 = 54% RECANALISED						
TOTAL ALL PATIENTS = 363/594 = 61% RECANALISED						

Studies are listed according to drug used and increasing dose. "Number of patients" refers to total number of patients in the study. UK=urokinase, SK=streptokinase, tPA= tissue-type Plasminogen Activator. IA = intraarterial, IV = intravenous route of drug administration. ASSG = Acute Stroke Study Group

Table 4.1.2 : "Open studies of Thrombolysis for Acute Ischaemic Stroke : Recanalisation

"Open" Studies of Thrombolysis for Acute "Ischaemic" Stroke : Clinical Outcome

Author	Year	Drug	Route	Dose	Number of patients	% improved clinically
Del Zoppo(399)	1988	SK	IA	0.6-2.5x10 ⁵ u	20	75
Theron(381)	1989	SK	IA	0.25-1.5x10 ⁵ u	12	83
Berg-Dammer(397)	1991	SK	IA	10 ⁵ u	3	100
Maisa(400)	1988	SK	IA	1-2.5x10 ⁵ u	15	73
TOTAL FOR SK = 39 / 50 = 78% IMPROVED						
Terashi (428)	1990	UK	IV	6x10 ⁴ u/day for 7 days	171	35
Yamaguchi(403)	1991	UK	IV	6x10 ⁴ u/day for 7 days	77	45
Abe(382)	1981	UK	IV	6x10 ⁴ u/day for 7 days	51	70
Fukase(420)	1972	UK	IV	10 ⁴ -10 ⁵ u	949	68
Mori (277)	1990	UK	IA	1.8-3.2x10 ⁵ u	22	55
Lehman(395)	1989	UK	IA	2-3x10 ⁵ u	10	70
Fujishima(405)	1986	UK	IV	3x10 ⁵ u	143	79
Ikeda(396)	1990	UK	IA	4.2x10 ⁵ u	13	53
Mobius(398)	1989	UK	IA	2x10 ⁵ u	14	71
Mihara(421)	1982	UK	IV	3x10 ⁵ u	33	78
Abe(382)	1981	UK	IV	6x10 ⁵ u/day for 7 days	49	80
Berg-Dammer(397)	1991	UK	IA	2-7.5x10 ⁵ u	7	57
Seipman(379)	1991	UK	IA	7.5x10 ⁵ u	11	64
Zeumer(429)	1985	UK/ SK	IA	various	29	59
Zeumer(401)	1989	UK	IA	2.5-7.5x10 ⁵ u	7	57
Matsumoto(374)	1991	UK	IA	2.4-12x10 ⁵ u	52	59
Miyakawa(375)	1984	UK	IV/IA	7-9x10 ⁵ u	49	45
Williams (423)	1992	UK	IA	5-10x10 ⁵ u	3	33
Fletcher(402)	1976	UK	IV	1.4-3.3x10 ⁶ u	31	52
Nenci(406)	1983	UK	IV	1.7x10 ⁶ u	4	75
Labauge(407)	1978	UK	IV	6-34.5x10 ⁵ u	24	42
TOTAL FOR UK = 1133/ 1747 = 65% IMPROVED						
Terashi (428)	1990	tPA	IV	3.6x10 ⁴ AKU/day for 7 days	171	59
Ohtomo (384)	1988	tPA	IV	3.6-6x10 ⁴ AKU/day for 7 days	131	69
Yamaguchi(403)	1991	tPA	IV	1.7-3.4mg/day for 7 days	145	66
NIH Study(372)	1991	tPA	IV	50-70mg	94	26
Hennerici(373)	1991	tPA	IV	70mg	18	28
von Kummer(404)	1991	tPA	IV	70or100mg	27	35
Overgaard(430)	1992	tPA	IV	100mg	21	85
Brucker (425)	1992	tPA	IV/IA	100mg	28	29
von Kummer (426)	1992	tPA	IV	100mg	32	44
TOTAL FOR tPA = 373/ 667 = 56% IMPROVED						
TOTAL ALL PATIENTS=1545/2464 = 63% IMPROVED						

Table 4.1.3 : "Open" Studies of Thrombolysis for Acute Ischaemic Stroke : Clinical Outcome

Table 4.1.4 : Asymptomatic Intra-cerebral Petechial Haemorrhage Following Thrombolysis for Acute Ischaemic Stroke.

Author	Year	Drug	Route of admin.	Dose	Number of patients	% Affected
Del Zoppo(399)	1988	SK	IA	0.06-2.5 $\times 10^5$ u	20	20
Zeumer(394)	1984	SK	IA	1.25×10^5 u	2	50
Theron(381)	1989	SK	IA	$0.25-1.5 \times 10^5$ u	12	16
Berg-Dammer(397)	1991	SK	IA	10^5 u	3	0
Maisa(409)	1988	SK	IA	2×10^5 u	16	0
Hacke(363)	1988	SK	IA	4×10^5 u	45	5
Frink(409)	1990	SK	IV	1.5×10^6 u	1	0

TOTAL FOR SK 9/97 = 9.2% PETECHIAL HAEMORRHAGE

Yamaguchi (403)	1991	UK	IV	6×10^4 u/day for 7 days	77	5
Ohtomo(354)	1985	UK	IV	6×10^4 u/d for 7 days	169	1
Harembert(410)	1979	UK	IA	1.5×10^5 u	1	0
Mori(277)	1990	UK	IA	$1.8-3.3 \times 10^5$ u	43	12
Jungreis(411)	1989	UK	IA	2.1×10^5 u	1	0
Lehmann(395)	1989	UK	IA	$2-3 \times 10^5$ u	10	0
Fujishima(405)	1986	UK	IV	3×10^5 u	143	0
Ikeda(396)	1990	UK	IA	4.2×10^5 u	13	0
Casto (427)	1992	UK	IA	5.6×10^5 u	5	20
Berg-Dammer(397)	1991	UK	IA	$6-7 \times 10^5$ u	10	20
Seipman(379)	1991	UK	IA	7.5×10^5 u	11	30
Zeumer(401)	1989	UK	IA	7.5×10^5 u	7	14
Abe(365)	1984	UK	IV	$6-12 \times 10^5$ u	62	0
Seikmann(380)	1991	UK	IA	8×10^5 u	2	0
Miyakawa(375)	1984	UK	IA/IV	$7-9 \times 10^5$ u	49	26
Matsumoto(374)	1991	UK	IA	$2.4-12 \times 10^5$ u	52	20
Nenci(406)	1983	UK	IV	1.7×10^6 u	4	0

TOTAL FOR UK = 46/867 = 5% PETECHIAL HAEMORRHAGE

Yamaguchi (403)	1991	tPA	IV	1.7-3.4mg/day for 7 days	145	0
Yamaguchi(403)	1991	tPA	IV	17-51mg	58	21
ASSG (278)	1991	tPA	IV	12.5-44mg	104	20
Bruckmann (412)	1989	tPA	IV	25.9mg	1	100
Okada (364)	1991	tPA	IV	26-56mg	15	33
JTSG(356)	1992	tPA	IV	34mg	51	39
Mori (276)	1991	tPA	IA	34 or 50mg	19	66
Buteux(413)	1988	tPA	IA	50mg	1	100
NIH Study(372)	1991	tPA	IV	50-70mg	94	10
von Kummer(404)	1991	tPA	IV	70/100mg	27	22
von Kummer(426)	1992	tPA	IV	100mg	32	28
Turrin(414)	1991	tPA	IV	100mg	1	0
Overgaard(430)	1992	tPA	IV	100mg	21	0
Wildemann(415)	1990	tPA	IV	100mg	1	0
Herderschee(416)	1991	tPA	IV	100mg	2	50
Henze (1)	1987	tPA	IA	100mg	1	0
Brucker (425)	1992	tPA	IV	100mg	28	25
Jafar (431)	1991	tPA	IV	150mg	1	0

TOTAL FOR tPA = 101/582 = 17% PETECHIAL HAEMORRHAGE

GRAND TOTAL ALL DRUGS = 156/1546 = 10% PETECHIAL HAEMORRHAGE

Table 4.1.5 : Intra-cerebral Haematoma with Clinical Deterioration Complicating Thrombolysis for Acute "Ischaemic" Stroke.

Author	Year	Drug	Route of Admin.	Dose	Number of patients	% Affected
Sussman (351)	1958	F	IV/IA	various	3	0
Clark (417)	1960	F	IV/IA	2-10x10 ⁵ u	10	0
Meyer (352)	1963	T	IV	2x10 ⁵ u	20	5
Atkin (418)	1964	F	IA	5x10 ⁵ u	1	0
Del Zoppo (359)	1988	SK	IA	0.6-2.5x10 ⁵ u	20	0
Theron (381)	1989	SK	IA	0.25-1.5x10 ⁵ u	12	8
Berg-Dammer (397)	1991	SK	IA	10 ⁵ u	3	0
Maisa (400)	1988	SK	IA	2x10 ⁵ u	16	6
Hacke (363)	1988	SK	IA	4x10 ⁵ u	45	4
Meyer (353)	1964	SK	IV	2.5-7.5x10 ⁵ u	37	3
Frink (409)	1990	SK	IV	1.5x10 ⁶ u	1	0
TOTAL for SK = 7/135 = 5% CEREBRAL HAEMATOMA						
Yamaguchi (403)	1991	UK	IV	6x10 ⁴ u/d for 7 days	77	1
Ohtomo (354)	1985	UK	IV	6x10 ⁴ u/d for 7 days	169	0
Abe (382)	1981	UK	IV	6-60x10 ⁴ u/d/7d	101	1
Hass (419)	1966	UK	IA	10 ⁵ u	1	100
Harembert (410)	1979	UK	IV	1.5x10 ⁵ u	1	0
Mori (277)	1990	UK	IA	1.8-3.2x10 ⁵ u	43	9
Jungreis (411)	1989	UK	IA	2.1x10 ⁵ u	1	0
Lehman (395)	1989	UK	IA	2-3x10 ⁵ u	10	0
Mihara (421)	1982	UK	IV	3x10 ⁵ u	33	0
Fujishima (405)	1986	UK	IV	3x10 ⁵ u	143	0.6
Ikeda (376)	1990	UK	IA	4.2x10 ⁵ u	13	23
Casto (427)	1992	UK	IA	5.6x10 ⁵ u	5	0
Berg-Dammer (397)	1991	UK	IA	2-7.5x10 ⁵ u	7	0
Abe (365)	1984	UK	IV	6-12x10 ⁵ u	86	1
Abe (232)	1981	UK	IV	6x10 ⁴ u/d for 7 days	106	0.9
Seipmann (379)	1991	UK	IA	7.5x10 ⁵ u	11	0
Zeumer (401)	1989	UK	IA	7.5x10 ⁵ u	7	0
Seikmann (380)	1991	UK	IA	8x10 ⁵ u	2	0
Matsumoto (374)	1991	UK	IA	2.4-12x10 ⁵ u	52	12
Fletcher (402)	1976	UK	IV	1.4-3.3x10 ⁶ u	31	12
Nenci (406)	1983	UK	IV	1.7x10 ⁶ u	4	0
Larcan (366)	1977	UK	IV	1.2-2.4x10 ⁶ u	36	0
Labauge (407)	1978	UK	IV	6-34x10 ⁵ u	37	0
Miyakawa (375)	1984	UK	IV/IA	7-9x10 ⁵ u	49	4
TOTAL for UK = 26/1025 = 3% CEREBRAL HAEMATOMA						
Yamaguchi (403)	1991	tPA	IV	1.7-3.4mg/d for 7 d	145	0
ASSG (278)	1991	tPA	IV	12.2-44mg	104	11
Karnik (424)	1992	tPA	IA	20mg	1	0
Bruckmann (412)	1989	tPA	IV	25.9mg	1	0
Yamaguchi (403)	1991	tPA	IV	17-51mg	58	15
Okada (364)	1991	tPA	IV	26-50mg	15	46
JTSG (356)	1992	tPA	IV	34mg	51	8
Mori (276)	1991	tPA	IV	34/50mg	19	10
Buteux (413)	1988	tPA	IA	50mg	1	0
NIH Study (372)	1991	tPA	IV	50-70mg	94	5
Hennerici (373)	1991	tPA	IV	70mg	18	5
vonKummer (404)	1991	tPA	IV	70/100mg	27	5
von Kummer (426)	1992	tPA	IV	100mg	32	9
Overgaard (430)	1992	tPA	IV	100mg	21	5
Turrin (414)	1991	tPA	IV	100mg	1	0
Wildemann (415)	1991	tPA	IV	100mg	1	0
Herderschee (416)	1991	tPA	IV	100mg	2	0
Henze (1)	1987	tPA	IA	100mg	1	0
Brucker (425)	1992	tPA	IV	100mg	28	4
Jafar (431)	1991	tPA	IV	150mg	1	0
TOTAL for tPA = 48/621 = 8% CEREBRAL HAEMATOMA						
GRAND TOTAL ALL DRUGS = 81/1781 = 5% CEREBRAL HAEMATOMA						

Severe Cerebral Infarct Oedema following Thrombolysis for Acute Ischaemic Stroke.

Author	Year	Drug	Route	Dose	Number of patients	% affected
Theron (381)	1989	SK	IA	0.25-1.5 $\times 10^5$ u	12	8
Fujishima (403)	1986	UK	IV	3×10^5 u	143	0.7
Ikeda (396)	1990	UK	IA	4.2×10^5 u	13	8
NIH Study (372)	1991	tPA	IV	50-70mg	74	3
Von Kummer (404)	1991	tPA	IV	70/100mg	21	33
Koudstaal (331)	1988	tPA	IV	100mg	2	100
Mori (276)	1991	tPA	IV	34-50mg	19	26

TOTAL = 18/284 = 6% SEVERE INFARCT OEDEMA

Note that severe infarct oedema was diagnosed by routine CT scan, and only studies which mentioned it as a complication have been included in the above table. "Number of patients" refers to total number of study patients. None of the above were randomised trials. SK = streptokinase, UK = urokinase, tPA = tissue plasminogen activator, IA = intraarterial, IV = intravenous.

**Table 4.1.6 : Severe Cerebral Infarct Oedema Following
Thrombolysis for Acute Ischaemic Stroke.**

THROMBOLYSIS FOR ACUTE "ISCHAEMIC" STROKE THROMBOLYSIS vs CONTROL: MORTALITY

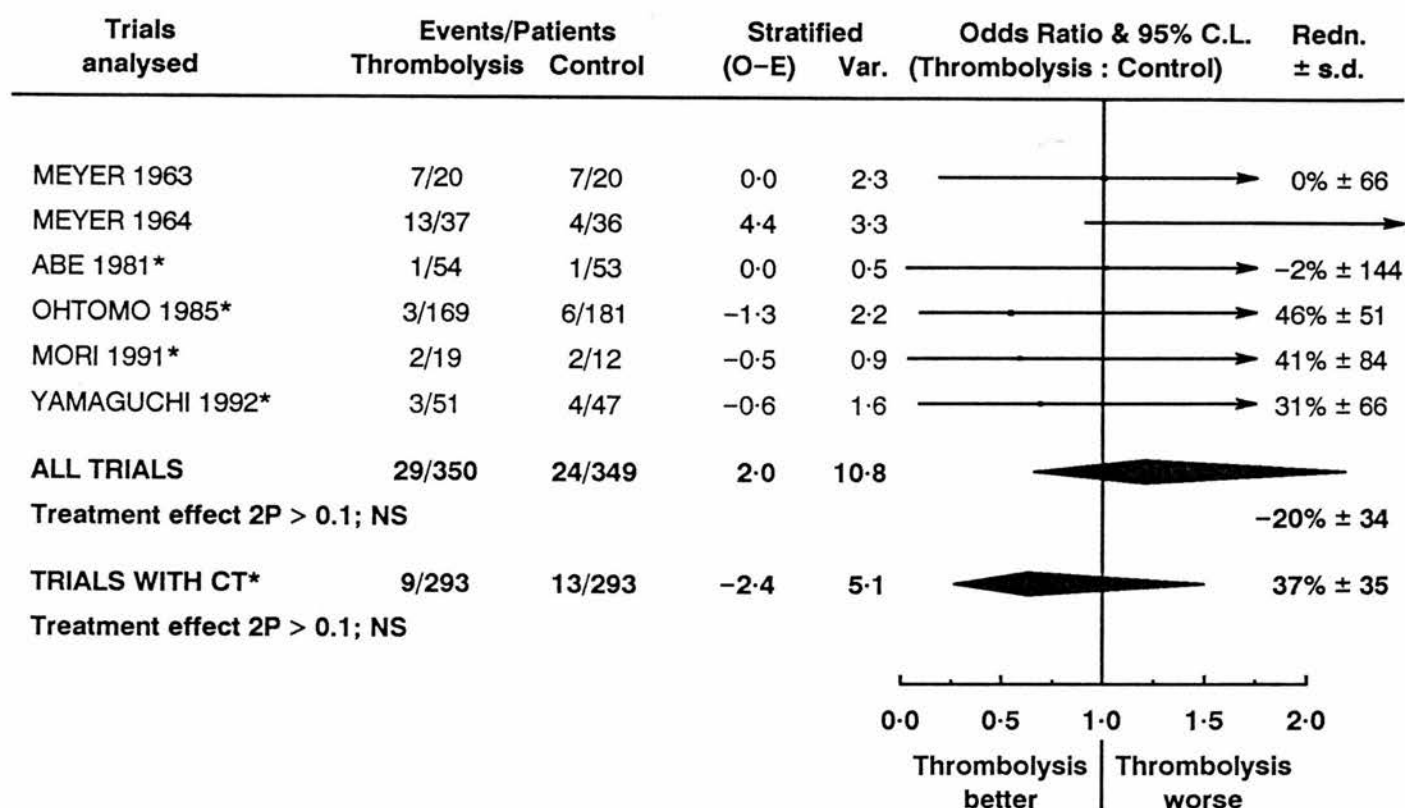


Figure 4.1.1 A Overview analysis of death following the use of thrombolytic drugs to treat acute "ischaemic" stroke. Note that the two trials by Meyer were done without the benefit of CT scanning to exclude cerebral haemorrhage as the cause of symptoms prior to treatment. "Yamaguchi" refers to the Japanese Thrombolysis Study Group trial. O-E = observed minus expected number of events in the treated group; Var = variance; Redn = reduction. An odds ratio of less than 1 indicates that thrombolytic treatment may be beneficial, and the 95% confidence interval gives the range of possible therapy effects. Meyer 1963(352), Meyer 1964(353), Ohtomo(354), Abe(355), Mori(276), Yamaguchi (356).

THROMBOLYSIS FOR ACUTE "ISCHAEMIC" STROKE **THROMBOLYSIS vs CONTROL: DEATH OR DETERIORATION**

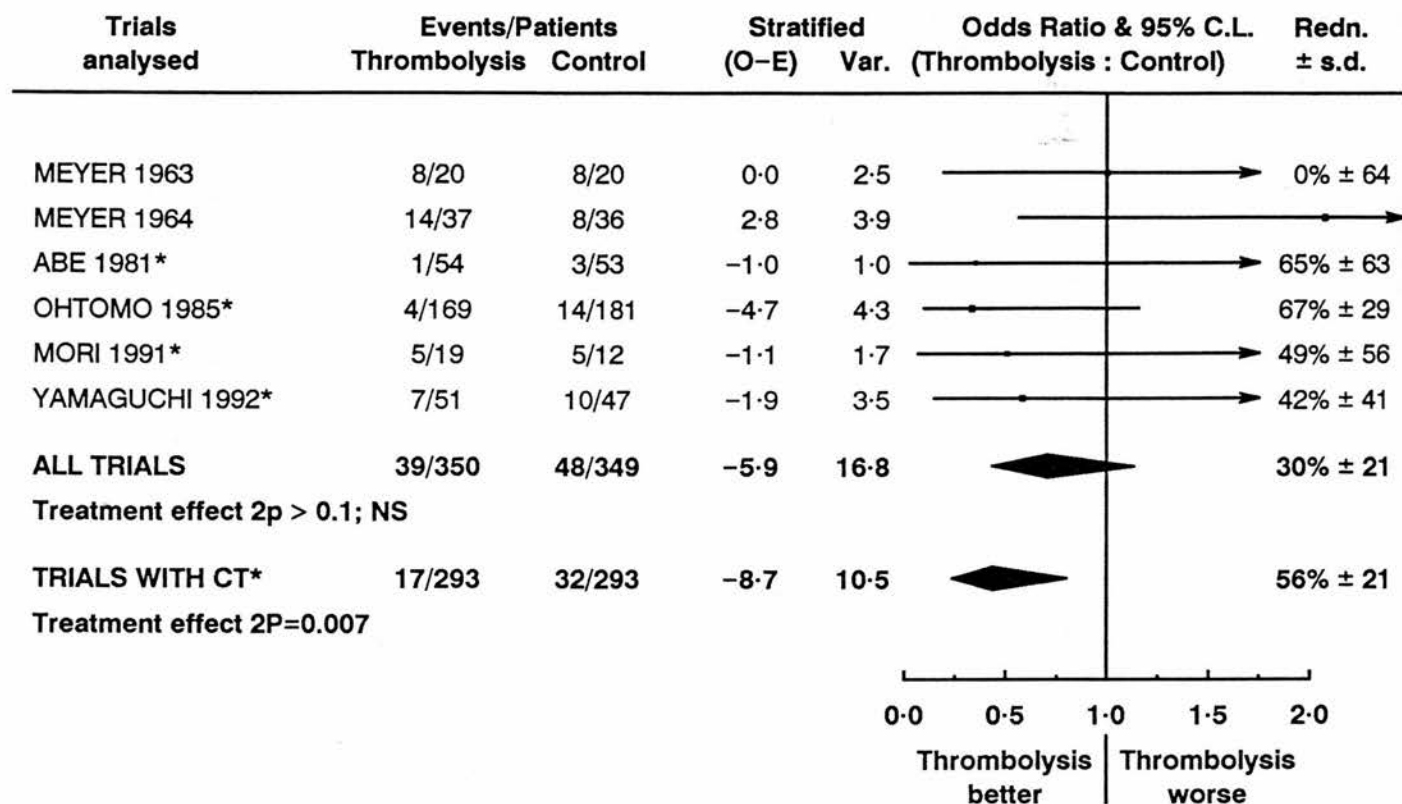


Figure 4.1.1 B Overview analysis of death or deterioration following the use of thrombolytic drugs to treat acute ischaemic stroke. see Legend Figure 4.1.1.A for interpretation and references.

Intracerebral Haemorrhagic Complications following Thrombolysis for Acute Ischaemic Stroke

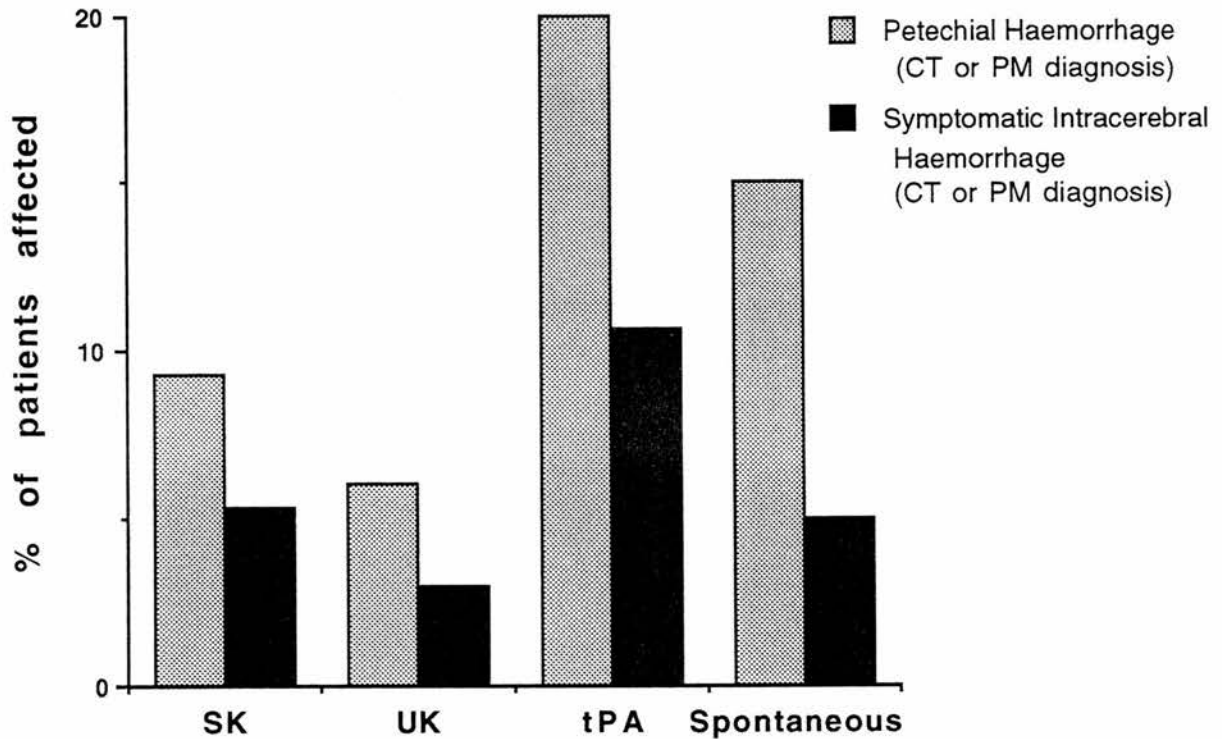
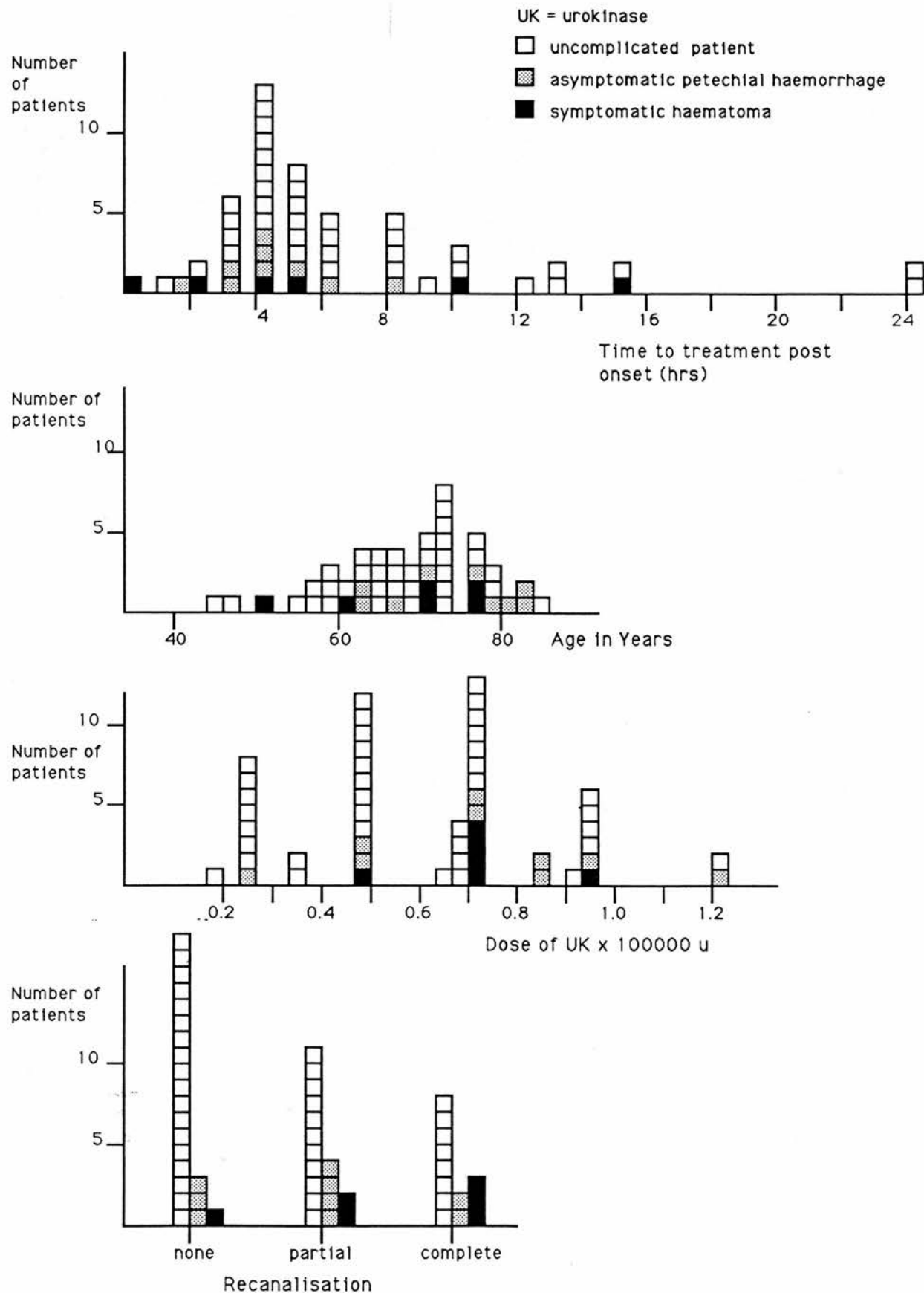


Figure 4.1.2 Comparison of the spontaneous rate of haemorrhagic transformation of the cerebral infarct with that following the use of thrombolytic drugs in acute ischaemic stroke. See Tables 4.1.4 and 4.1.5 for exact figures. SK = streptokinase, UK = urokinase, tPA = tissue Plasminogen Activator. The spontaneous rate is an estimate based on the rates of haemorrhagic transformation found in the prospective studies which used CT scanning. It is no more than a "best guess" and the limitations of the studies of haemorrhagic transformation have been discussed in Part One Chapter Six. Note that all reports of thrombolysis have been included in this figure, not just the randomised studies.

Figure 4.1.3 Data from Matsumoto.(374)



Part Four

Chapter Two

The Edinburgh Pilot Randomised Controlled Trial of Thrombolysis in Acute Ischaemic Stroke : Methodology and Protocol.

4.2.1 Introduction

4.2.2 Ethical approval

4.2.3 Study population and inclusion criteria

4.2.4 Mode of administration of thrombolysis

4.2.5 Time limit to treatment

4.2.6 Which drug

4.2.7 Dose of drug

4.2.8 Exclusion criteria

4.2.9 Imaging pre-randomisation

4.2.10 Consent and randomisation procedures

4.2.11 Angiography and treatment infusion

4.2.12 Medical staff responsibility for the patient

4.2.13 Clinical follow up

4.2.14 Imaging follow up

Summary of Chapter Two

4.2.1 Introduction

When this trial was first thought of, the idea of treating acute ischaemic stroke with thrombolytic drugs was considered to be a little unusual. A history of cerebrovascular disease is a standard contraindication to the use of thrombolytic drugs in acute myocardial infarction because of the theoretical risk of cerebral haemorrhage. And yet when looked at objectively, there are two good reasons why this attitude about thrombolysis as a treatment for acute ischaemic stroke may be wrong.

Firstly the evidence to date suggests that understanding of the natural history of acute ischaemic stroke is poor with respect to the frequency of haemorrhagic transformation of the infarct and severe infarct oedema, and why some patients (and how many) recanalise and not others. It is assumed that a drug which causes cerebral haemorrhage when used to treat other conditions may have devastatingly bad effects when used in acute stroke. Ignorance about the natural history of acute ischaemic stroke is mainly due to (until recently) the lack of practical techniques with which to investigate it, and the lack of any proven treatment to stimulate interest among the medical profession generally.³⁸⁹ These investigative tools are now available (CT brain scanning, non-invasive vascular imaging), and they should start to be used more systematically to answer these questions.

Secondly, acute ischaemic stroke is an occlusive vascular disease, so why should a drug which has been shown to work for occlusive vascular disease elsewhere in the body^{359,360,370,371,376} (myocardial infarction) not also be effective in treating acute cerebrovascular occlusive disease?

The need to find a treatment for acute ischaemic stroke is increasing as our population ages.^{65,348,390} A treatment which reduced disability by even a modest amount such as 10% to 20% would be worthwhile as acute ischaemic stroke is so common. It was with these thoughts in mind that the Edinburgh Pilot Thrombolysis Trial was started. A randomised controlled trial was obviously essential because the natural history and complications of acute ischaemic stroke (spontaneous recanalisation, haemorrhagic transformation of the infarct and severe infarct oedema) mimic the likely beneficial and adverse effects of thrombolytic treatment.

Information about acute ischaemic stroke and attitudes to treatments change very rapidly. At the time of setting up the trial in 1989 and early 1990, the concept of thrombolysis in stroke was so new that decisions about the trial protocol had to be made using the scant information available and a large amount of common sense (which could be less generously described as guess work). To try to give a flavour of the debate which took place between involved parties at the time, the major issues of the trial design -

type of patient to be included, end point analysis, investigations, mode of administration of thrombolysis, time window to treatment, etc, will be discussed in detail below.

4.2.2 Ethical approval

In some ways this was the easiest part of the organisation of the whole project. Approval for the study was granted, without any objection, by the Lothian Area Ethics of Medical Research Subcommittee, for a randomised controlled trial of intraarterial streptokinase 250000 units or placebo (saline), with cerebral angiography, in patients with extensive acute ischaemic stroke, in January 1990.

4.2.3 Study population and inclusion criteria

Because so little was known about the risk of thrombolytic treatment in the acute stages of a stroke, it was decided that only patients whose prognosis was already poor with current management ie TACI and possibly large PACI strokes should be included.²⁵ The work of AR Naylor on validating the MCTT technique in the Western General Hospital,³⁰⁹ suggested that the number of patients with severe strokes admitted to the Western General Hospital would be small (no other reliable information on number of stroke patients admitted to the hospital was available at the time), so it was unlikely that a local trial would demonstrate conclusively any clinical effect (ie improved

outcome) of thrombolytic treatment. Little was known about the behaviour of acute cerebral embolic and thrombotic occlusions. There is a natural lysis rate of presumed embolic cerebral arterial occlusions of approximately 20% at 24 hours after stroke onset,^{119,122,125} but this may depend on the type of occlusion, where it is, what its origin was (eg atheroma from the cervical carotid artery or cardiogenic embolus), so it was considered important to find out more about the response of cerebrovascular occlusions to thrombolytic therapy.

Occlusive lesions in the cerebral circulation may behave differently to those in the coronary circulation. The latter are predominantly due to fresh thrombus forming on an acutely ruptured atheromatous plaque.³⁵⁹ If thrombolytic drugs cannot lyse cerebral artery occlusions then they are unlikely to have much impact on clinical outcome. There were no randomised controlled trials examining lysis rates, only dose range finding studies where all patients received thrombolytic treatment. It was therefore decided to start by examining the surrogate endpoint of recanalisation primarily, and clinical outcome secondarily, thus gaining experience of the use of thrombolysis in stroke.

A power calculation indicated that 30 patients would be needed to demonstrate improved lysis of the cerebral artery occlusion from the expected 20% spontaneous rate to 60% with thrombolysis, and fewer patients if thrombolytic

treatment was more effective. The 60% estimate of possible thrombolytic effect was based on a) the result of the literature review of thrombolysis in stroke in which the small non-randomised angiographic studies suggested that thrombolysis might result in a 60% arterial recanalisation rate (Table 4.1.2), and b) the intraarterial thrombolysis in myocardial infarction trials which also found a recanalisation rate of around 60% following thrombolysis (Part Four Chapter One). More patients would be required if the true recanalisation rate was actually lower.

As stroke is a disease mainly affecting the elderly, it was considered inappropriate to have an upper age limit, but a lower age limit of 18 years was set because of the need to obtain informed consent for patients randomised in the trial.

The other inclusion criteria were that patient had to be independant prior to their stroke, and be able to give consent to enter the trial (or have a relative who could act for them). Patients with a history of previous stroke were still eligible for the trial as long as there was no residual disability. The patients were to be carefully examined by a stroke neurologist and classified according to the OCSF clinical classification.²⁵ They must have either a TACI or large PACI acute ischaemic stroke. A CT brain scan was essential to exclude cerebral haemorrhage or tumour as the cause of stroke symptoms (see below).

4.2.4 Mode of administration of thrombolysis

There was considerable debate among interested parties about the merits and demerits of intra-arterial and intravenous treatment. Although intravenous administration was more practical and quicker, a larger dose of thrombolytic drug (probably 1.5 MU) would be required compared with the intraarterial dose (250000 U) based on information from the myocardial infarction trials.^{359,369} There was great concern that the larger dose would result in greater risk of haemorrhagic transformation of the infarct, as well as of systemic adverse effects, with adverse effects on outcome. Clearly if recanalisation was to be the trial endpoint, a reliable method of demonstrating this would be required, convincing to doctors in other centres, not just those participating in the trial. As this was a preliminary study, and at the time the only truly reliable method of demonstrating cerebral arterial pathology was angiography, the surrogate endpoint of recanalisation required angiography to ascertain treatment effect. With a catheter in the symptomatic cerebral artery, it was reasonable to administer the thrombolytic drug intraarterially, enabling the lower dose to be used and perhaps also reducing the risk of adverse effects.

In the future, practical treatments for acute is-

chaemic stroke should be administered in the simplest possible way to reduce time delays. Thrombolysis, if it works and becomes available for treatment of acute ischaemic stroke, would be administered more practically and quickly by the intravenous route. It was not the intention in this trial to advocate intraarterial treatment of acute ischaemic stroke, but simply to assess its efficacy in recanalising occluded cerebral arteries.

4.2.5 Time limit to treatment

Most recent "trials" (non-randomised) of thrombolysis have had a six hour onset-to-treatment time limit, stating that previous "trials" of thrombolytic treatment had found an increased rate of cerebral haemorrhage if treatment was given after six hours. No evidence of this was found in the extensive search of the literature, but several largely anecdotal examples of thrombolytic treatment after six hours not causing increased haemorrhagic transformation of the infarct were found.^{374,375}

Most suspected acute ischaemic stroke patients in the UK go to hospital in a "slow ambulance", so few reach hospital under six hours. It is unrealistic to expect referral patterns to change in the near future, and there will always be stroke patients who reach hospital late because they live alone and have to wait until someone finds them, and there

are those who awake with their stroke symptoms. In both groups the time of onset may be uncertain. For these reasons it was considered important to study the ability of thrombolysis to lyse cerebral arterial occlusion and get some idea of the risks and benefits of thrombolytic treatment up to 24 hours after stroke onset. It was decided that patients should be included up to 24 hours after onset of symptoms, to allow for those who awake with a stroke, and stratified the randomisation into three groups : "under six hours", "six to twelve hours", and "twelve to 24 hours" after symptom onset.

4.2.6 Which Drug ?

There was considerable information about the risks and benefits of the main thrombolytic drugs from their use in the myocardial infarction trials,^{359,360,369} although the trials comparing the commonly available thrombolytic drugs directly had not been completed.^{370,371,376} Streptokinase (SK) was the least expensive (£85.00 per treatment for MI), then urokinase (UK), then tPA (£816.00 per treatment for acute MI). SK was slightly less effective than tPA at recanalising acute coronary occlusions (though reocclusion was more frequent with tPA),^{350,377} but it was felt at the time of starting the pilot stroke trial there was insufficient evidence of increased clinical benefit to justify the ten

times increased cost of tPA instead of SK. Urokinase is more widely used in Europe, and has the advantage of being non-allergenic, but there was little experience of its use in the UK, and it was more expensive than streptokinase. For these reasons it was decided that SK should be used in the pilot stroke trial. Table 4.2.1 compares the properties of the commonly available thrombolytic drugs.³⁵⁰

The choice of drug has since been supported by the ISIS-3 and GISSI-2 results.^{370,371,376} In these large trials in acute MI (60000 patients combined), both tPA and streptokinase produced the same clinical benefit in terms of reduction in vascular death. However there was a highly significant excess of intracerebral haemorrhage with tPA: 7 per 1000 patients treated instead of 3 per 1000 patients treated with streptokinase.

4.2.7 Dose of Drug

The behaviour of thrombolytic drugs, particularly SK, in an individual is unpredictable, mainly due to the presence of cross reacting antibodies from streptococci.^{350,377} These may reduce the efficacy of the SK and consequently in acute myocardial infarction, a large dose (1.5 million IU) given intravenously is standard. There have been few dose-range-finding studies for acute myocardial infarction. The earlier studies used intracoronary

administration, and 250000 IU was found to be effective.^{350,369} 500000 to 1.5 million IU have been used for intravenous administration. On the same principal, and to keep potential systemic adverse effects to a minimum, it was decided that 250000 IU of SK should be used intraarterially. This may be inadequate, although haematological studies have shown that this amount is sufficient to induce systemic fibrinolysis in 90% of individuals.³⁷⁷ The thrombolytic effect of SK lasts for up to 24 hours, so it was felt that this was a reasonable dose to start the pilot stroke trial with.

4.2.8 Exclusion criteria

The exclusion criteria were as follows:

- SK treatment more than five days or less than one year previously (because of the risk of allergic reactions)
- pregnancy or recent childbirth
- active peptic ulceration
- recent trauma or surgery
- bleeding diathesis
- anticoagulant treatment (warfarin)
- other serious medical condition which on its own would have made survival beyond three months unlikely
- hypertensive (diastolic < 110 mmHg)
- symptoms obviously improving since onset, ie likely to be a TIA.

4.2.9 Imaging Tests Pre-Randomisation

All patients must have had a CT brain scan to exclude a cerebral haemorrhage or other non stroke pathology as the cause of symptoms. At the beginning of the study, it was also thought that there should be no visible recent infarct on the CT scan because of a suggestion from previous "trials" of thrombolysis in acute ischaemic stroke of an increased risk of haemorrhagic transformation if patients who already had a cerebral infarct visible were given thrombolysis. Again, as with the time limit to treatment, the objective evidence for this was lacking. Although frequently stated in previous "trials" of thrombolysis that it was dangerous to use thrombolysis if an infarct was already visible, no data could be found to support this. However it seemed prudent at least at the start of the trial, to exclude patients with obvious areas of recent infarction visible likely to be the symptomatic lesion. The protocol was later changed to exclude patients only if there was haemorrhage visible (or another cause of symptoms such as a tumour) as it quickly became apparent that even the patients we scanned very early after symptom onset had a new infarct visible, so it was unrealistic to exclude them.

Transcranial Doppler was performed to confirm vessel

occlusion, and an MCTT if time and isotope availability permitted. If the symptomatic MCA had a normal blood velocity and was likely to be patent then the patient was excluded from the trial, as I did not wish to expose patients likely to have a patent MCA to the risk and discomfort of angiography. If there was any doubt about the accuracy of the TCD result, for example if the patient was restless or there was a poor temporal bone window, then the patient was included. Ideally these patients should have had an MCTT study, but at the time of starting the pilot trial, the gamma camera and computer processing set up mean that although the transit time data can be acquired in the Neuroradiology Department, it had to be processed in the Nuclear Medicine Department computer in a different part of the hospital. This would have involved an extra half hour time delay to randomisation. If the data processing could have been done in the Neuroradiology Department, the entire MCTT study would take ten to fifteen minutes, comparable to the time taken to perform TCD.

4.2.10 Consent and randomisation procedures

If the trial inclusion criteria were satisfied, the patient's or a close relative's consent was sought. A copy of the consent document is included in Appendix Seven. This must have been signed by the patient, or relative, and the doctor explaining the trial procedure. The consent procedure

was kept as simple as possible similar to the consent procedure for ISIS-2.³⁶⁰ A patient, or the relative of a patient, who has just suffered a stroke is likely to be confused, frightened, and unable to take in a complicated explanation of trial procedure. The patients were likely to be dysphasic if the infarct was in the left hemisphere, and possibly unaware of their deficit if the infarct was in the right hemisphere. The consent procedure adopted for the pilot trial concentrated on the lack of any treatment for stroke at the moment, the fact that clot-dissolving treatments work in heart attacks and showed promise in stroke, but that it was uncertain if the benefits outweighed the risks. The patient, or relative, was given plenty of opportunity to ask questions about the trial before consenting to take part and also encouraged to ask about anything of concern at any time thereafter.

The patient was prepared for angiography. Ready prepared, serially numbered, randomisation packs containing everything required to make up a dose of SK or placebo were kept in a fridge next to the angiography suite. One of these was selected depending on which randomisation group the patient fell into (0-6, 6-12, 12-24 hours) and given to a house officer or non-trial member of medical staff to make up and bring to the angiogram suite. These packs were made of opaque black plastic and contained an instruction sheet, a fifty ml bag of normal saline, needles, a five ml syringe,

a mediswab, and either a box containing a vial of 250000IU SK or a box containing an empty glass vial of similar weight. From the outside the packs appeared identical and were simply marked with the sequential randomisation numbers. The treatment infusion was prepared by a doctor not directly involved in the trial such as the Neurology house officer, into the fifty ml bag of saline, and passed to the nurse assisting with the angiogram without telling the radiologist or trial neurologist whether the bag contained SK or the saline placebo. This was to ensure blinding of the doctors directly involved in the trial to reduce bias as much as possible. Care had to be taken by the doctor making up the infusion, as SK being a protein froths in solution, to ensure that not too many air bubbles developed. The nurse assisting with the angiogram procedure drew up the prepared infusion into a 50 ml syringe taking care to exclude all air bubbles, and handed it to the radiologist, who infused it intraarterially. The materials from the infusion randomisation pack were replaced in the pack by the doctor making up the infusion, the pack was sealed and returned to Pharmacy who checked that the infusion had been correctly prepared.

The intention was to administer the infusion as blindly as possible. It was difficult to tell the difference between the placebo and treatment infusions unless the syringe was closely inspected, so this was as blind a method as could be devised without an actual placebo powder, which

would have been difficult to produce and very expensive.

4.2.11 Angiography and treatment infusion

If the clinical, CT and TCD criteria were met, and consent was given, the patient was prepared for angiography. An arterial introducer sheath was inserted under local anaesthetic, into the femoral artery (usually the right) and a diagnostic angiogram of the symptomatic carotid artery was performed. If an arterial occlusion was confirmed, the drug or placebo was infused into the occluded artery through the diagnostic catheter with the tip placed as close to the point of occlusion as possible. If the occlusion was in the MCA, a cerebral microcatheter would be placed through the diagnostic catheter and the tip advanced as close to the lesion as possible so that the treatment infusion could be given close to the occluding thrombus.

The angiogram of the symptomatic artery was repeated immediately after the treatment infusion had finished. The cerebral catheter was removed leaving the intra-arterial sheath in the femoral artery (to protect the puncture site from bleeding and to allow access for follow up angiography), and the patient transferred to the Neurology Ward for careful nursing care. Eighteen to twenty-four hours after the stroke onset, if the patient was well enough, the angiogram of the symptomatic artery was repeated. The cathe-

ter and sheath were removed, and the patient returned to the Neurology Ward for at least 24 hours for intensive post-angiography nursing care. If stable, the following day the patient was returned to the care of the General Medical staff in the General Medical Wards, where they would have gone directly after admission had they not entered the thrombolysis trial.

4.2.12 Medical staff responsibility for the patient

For the first 48 hours after randomisation, the patient was under the care of either Professor CP Warlow or Dr PAG Sandercock in the Neurology Ward. This arrangement was similar to the concept of a coronary care unit, where the patient spends the first few days of admission under the care of one Physician, and is then transferred to a General Medical Ward under the care of the Physician on whose acute receiving day he was originally admitted. We adopted this strategy after careful discussion with the General Physicians in our hospital, who were keen to remain nominally in charge of the acute stroke patient during the first few days after admission, but recognised the need for specialist medical and nursing care such as could be provided best in the Neurology Ward.

4.2.13 Clinical follow up

The patients were carefully monitored during and after angiography, with two-hourly neurological nursing observation (Glasgow Coma Scale) and standard post-angiography checks (BP, pulse, puncture site check).

For the trial assessment, the following were recorded (all described in detail in Appendix 8):

-Conscious level : Reaction Level Scale was used as this avoided the "pseudoscore" with the Glasgow Coma Scale which occurs with dysphasic patients (Appendix Eight).

-Motor Function : This was measured using the Motricity Index pre and post angiography, at three and fourteen days, and at three and six months.

-Disability : This was measured using the Oxford Handicap Scale (derived from the Rankin Scale) and the Barthel Index, both at 14 days, three and six months.

Unless there was a clear contraindication it was decided that the patients should start on aspirin 300 mg daily at 24 hours after the stroke, to be continued indefinitely.

4.2.14 Imaging follow-up

This was as follows:

-CT brain scanning : This was performed at 24 hours, three

and fourteen days, and whenever there was a new clinical indication such as falling conscious level. Standard non-contrast scan, ten mm slice interval only,

-TCD : Four hourly in the first 24 hours, daily for the first week, twice in the second week, and thereafter if indicated.

-MCTT : if performed pre-randomisation, at three and fourteen days.

Summary of Chapter Two

1. The philosophy behind the thrombolysis trial is described with emphasis on the points of major debate at the time of setting up the trial.
2. Patient inclusion and exclusion criteria are described.
3. Imaging criteria are described.
4. The consent and randomisation procedures are described.
5. The mode of administration of the treatment, and post treatment imaging and clinical follow up are described.

	SK	APSAC	UK	SCU-PA	RT-PA	
					2-CHAIN	1-CHAIN
Half-life (min)	23	90	16	7	8	5
Fibrin enhancement	1+	1+	2+	4+	4+	3+
Plasma proteolytic state	4+	4+	3+	2+	2+	1+
Duration of infusion	60 min	2-5 min	5-15 min	Several hours	Several hours	Several hours
Thrombus specificity (vs. hemostatic plug)	0	0	0	0	0	0
Incidence of reperfusion (% within 3 hr)	60-70	60-70	60-70	60-70	60-70	60-70
Speed of reperfusion (min)	45	45	45	45	45	45
Frequency of reocclusion (estimated %)	15	10	10	NA	20	20
Simultaneous administration of heparin	No	No	No	Yes	Yes	Yes
Bleeding complications	4+	4+	4+	4+	4+	4+
Allergic side effects	Yes	Yes	No	No	No	No
Antigenicity	Yes	Yes	No	NK	NK	NK
Expense	1+	2+	3+	4+	4+	4+

*SK denotes streptokinase, APSAC acylated plasminogen-streptokinase activator complex, UK urokinase, SCU-PA recombinant single-chain urokinase plasminogen activator, RT-PA recombination tissue-type plasminogen activator, NA data not available, NK not known, 0 none, and 4+ highest. The clinical data were derived mostly from reported experience with current intravenous dosages in the treatment of acute myocardial infarction.

Table 4.2.1 Comparative properties of commonly available thrombolytic drugs. From Marder.(350)

Part Four

Chapter Three

**Thrombolysis in Acute Ischaemic Stroke - Does It Work?
The Interim Results of the Edinburgh Pilot Thrombolysis
Trial : February 1991 to January 1992.**

4.3.1 General Results

4.3.2 Publicity

4.3.3 Randomised patients - Results

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Summary of Chapter Three

4.3.1 General Results

The pilot intraarterial thrombolysis trial was ready to start in late February 1991. The first patient was randomised on June 3rd 1991. All acute stroke patients admitted to the Western General Hospital were theoretically considered for the thrombolysis trial, but most of them had very obvious reasons for exclusion such as too mild a stroke, or other disabling illness. The patients who were very actively considered for randomisation but rejected, are listed in Table 4.3.1. The reasons for rejection will be discussed in detail below, as they are indicative of the type of problem encountered in trials of treatment for acute ischaemic stroke, particularly thrombolysis, and should be considered in future trial design.

The first patient randomised was the tenth patient actively considered for the trial. Prior to that, in the first three months of the trial, five patients had been excluded because an infarct was already clearly visible on the CT brain scan in the symptomatic area (although the patients were all scanned within or at six hours from symptom onset). It had been suggested in previous reports of non-randomised trials, that these patients were at high risk of haemorrhagic transformation following thrombolysis.^{357,364} Also the literature at the time suggested that infarcts were rarely seen under twelve hours from symptom onset.^{222,229,230,237} This was clearly not true. There was

so much concern about how much importance should be attached to early visibility of the infarct as a warning of increased cerebral haemorrhage risk after thrombolysis, that I took the CT scans of the five patients (considered for the trial but rejected because of infarct visibility) to the First International Meeting on Acute Stroke in Geneva in May 1991. There I was able to show the scans to Dr Okada, Dr Ringelstein, Dr Matsumoto, Professor Mori, Professor Hacke and Dr Deisenhammer, all of whom had published the results of small non-randomised trials of thrombolysis in stroke. There was total disagreement about a) whether or not an infarct was visible, and b) whether they would have included each patient in a thrombolysis trial on the strength of the appearance of the CT scan. Thereafter the trial protocol changed to use the CT scan just to exclude cerebral haemorrhage or tumour and to ignore the presence of visible infarction.

One patient was excluded because she had received streptokinase for a myocardial infarction eight days earlier. If thrombolysis were shown to work, then in this circumstance one could use a different thrombolytic drug such as urokinase, but in the context of a randomised trial, this was not possible.

The CT scanner broke down half way through the brain scan of another patient (number two), without obtaining views of the symptomatic area. The patient was not randomised in the thrombolysis trial, but she was randomised to

anticoagulant therapy in the International Stroke Trial.³¹⁴ The following day, when the CT scanner had been repaired, she was rescanned and had a primary intracerebral haemorrhage as the cause of symptoms, but despite (or because of) the anticoagulant treatment, her neurological state had improved quite dramatically in the intervening 24 hours!

In patient number five it proved impossible to obtain even a few diagnostic CT images because the patient had marked nausea, was restless and had continuous hemiballismic arm movements. He had a right hemisphere stroke and part of his non-cooperation was because of lack of awareness of his illness. The following day he was more settled and the CT scan revealed a large right MCA territory infarct, and an infarct of the left caudate nucleus. Several patients since then with large right hemisphere infarcts have also proved very difficult to manage because of incomprehension of their condition, lack of cooperation and restlessness. It may be that in order to investigate and treat these patients, heavy sedation and possibly a general anaesthetic is required, difficult to justify at the moment for an unproven treatment in the context of a trial. Perhaps once proven treatments for acute ischaemic stroke are available, anaesthetists will be more willing to administer sedative drugs in the acute phase of the stroke.

Only one patient (number eleven) had no relative available to discuss consent. It had been expected that

obtaining consent might be one of the most difficult and frequent problems in an acute stroke treatment trial. Many elderly people live alone, and dysphasia would be common, but most of the patients arrived at hospital accompanied by relatives, who were only too keen to have someone taking an interest, and understood the reasons for the trials. In another large hospital in our city, the majority of acute stroke patients do not even have a CT brain scan (Dr B Chapman, personal communication).

One patient (number fourteen) was inadvertently randomised into the International Stroke Trial after a telephone discussion of her clinical condition. On later review by medical staff with an interest in stroke, it became clear that her infarct was much more extensive than originally described, and she would have been suitable for the thrombolysis trial.

Another patient (number fifteen) was discussed within one hour of stroke onset, directly with the neurology registrar on call, and described by the GP as having a dense hemiparesis with dysphasia. When the patient arrived four hours after onset (she had been sent in a slow ambulance), she was found to have a mild partial hemiparesis and dysarthria making the stroke a LACI rather than a large PACI, and therefore unsuitable for the thrombolysis trial. In addition her symptoms had clearly improved between onset and arrival at hospital, and she would not have consented to angiogra-

phy. This illustrates one of the difficulties in distinguishing between lacunar and cortical infarcts which was encountered on several occasions, usually with junior medical staff or those who do not see stroke patients frequently, but difficulties can occur even with experienced stroke doctors (Part Two, Chapters Three and Four). Wider awareness of a simple classification such as the OCSF clinical classification might help reduce this problem.

Patient number sixteen with a medium sized PACI was randomised in the thrombolysis trial, but at angiography was found to have an incidental, unsuspected aneurysm arising from the intracavernous portion of the internal carotid artery, in addition to the peripheral MCA branch occlusion which was the cause of the stroke. Although there are anecdotal reports of patients with aneurysms being given thrombolytic drugs with no ill effect,³⁸⁰ the risks are not well quantified and it was not within the confines of the trial to give the patient an infusion which might increase the chances of aneurysm haemorrhage. The angiogram was terminated without giving the infusion, and the patient was randomised, uneventfully, in the IST.

On only one occasion was the "stroke team busy" and unable to assess the patient. The on call radiology cover for acute stroke trials was provided by myself (or Dr R Sellar for one week in December), and Dr Richard Lindley (or colleague on the few occasions when he was on holiday) for

clinical assessment. One occasion out of the entire year was not bad considering the domestic and other work commitments which we all have. If the treatment was of proven benefit, then normal out of hours medical cover would be provided as in coronary care units.

The final reason for failure to randomise more patients was time delay in between the patient reaching hospital and the stroke team being contacted. Two patients (numbers thirteen and nineteen) were simply not referred for over twelve hours, although one reached hospital one hour after onset, and the other at eight hours. They were simply overlooked, and this is in spite of considerable publicity for the stroke trials in the hospital. Several other patients waited in the Casualty Department for several hours before being referred. Patients were only considered for the stroke trials, or even imaging, with the consent of the Physician in charge of the case, so referral was discretionary.

4.3.2 Publicity

In order to raise awareness of the trials multiple publicity measures were initiated. Prior to the start of the trials, the background theory and protocols were presented at a Western General Hospital "Grand Round" at which most of the hospital medical staff were present. All new junior medical staff received a letter giving information about the

trials, and what to do in the event of discovering a stroke patient. Notices advertising the thrombolysis and International Stroke Trials were placed in the Casualty Department, the Medical Wards, Neurology Wards, and notice boards around the hospital. These notices gave clear instructions in the form of a flow diagram, of which patients are suitable and how to contact the stroke team. Other notices were put up giving instructions about a simple way to arrange CT scans and Carotid Duplex examinations on any patients (not just stroke patients). This was intended to make life easier for the busy junior medical staff, by replacing a trip to the Neuroradiology Department and a hunt for a Neuroradiologist to request a CT scan on a stroke patient, with a simple telephone call. Both Dr Lindley and I carried radiopagers and could be contacted at any time. Dr Lindley's was a "message pager" so a message could be sent with all relevant details obviating the need for the sender to wait for Dr Lindley to return their call. In addition Dr Lindley met the previous day's receiving medical registrar every weekday morning to find out about any stroke admissions during the previous 24 hours that he did not already know about. Despite all these measures there were still long delays in referral of patients to the stroke team, in some cases the patient reaching hospital more quickly than being referred once in hospital (Table 4.3.1).

In order to make life even easier for the receiving

medical staff, the Bed Bureau (a Health Board service which keeps track of hospital bed availability in the city and allocates patients to vacant beds) was asked to page Dr Lindley when a patient with a probable stroke had been referred to the Western General Hospital. He would check the Casualty Department periodically so that he often reached the patient before the receiving medical registrar. This improved referral times for patients coming through Bed Bureau, but not those who came direct to Casualty by ambulance after a 999 call.

In August 1991 the Western General Hospital Casualty Department closed so thereafter the Western General Hospital could only admit acutely ill patients referred by their GP through Bed Bureau, or transfers from other hospitals. The young acute stroke patients who tended to come direct to hospital after an ambulance 999 call, thereafter went to another large hospital in the city where the Casualty services became concentrated. This was a tragedy because there was little interest in acute stroke in that hospital, and many of the patients did not even have a CT brain scan to diagnose the cause of their stroke or assist with planning secondary prevention.

In the summer of 1991, publicity about the interest in acute stroke in the Western General, and the benefits that this can provide in terms of patient management, was increased by talking and writing to GPs in the Western

General Hospital catchment area. These measures all take time to work. In 1992/93 an acute stroke unit will be established in the Western General Hospital which, a bit like coronary care units, will raise awareness of the possibility of treating acute ischaemic stroke, and remove some of the complacent "there's no treatment so why do anything at all" attitude which prevails at present (Figures 4.3.1 A and B). Hopefully a happy medium, somewhere in between the scenarios depicted in these two Figures, will eventually be achieved.

4.3.3 Randomised Patients in the Streptokinase Trial

Five patients were randomised in 1991 of whom four received a treatment infusion. These will be described individually in chronological order. The patient who was randomised but did not receive the treatment infusion was the one described above who had an asymptomatic ICA aneurysm found on angiography.

Patient One : This 64 year old man was the tenth patient to be considered for the trial, and he very nearly was not included because a "public figure" was admitted with a subarachnoid haemorrhage the same morning and was due for angiography at the same time. Fortunately the patient with the subarachnoid haemorrhage was stable and it was possible to postpone their angiogram by several hours.

Clinical features: Patient One collapsed at 10.00 am and was found immediately by his wife. She made a "999" call, and he reached the WGH at 10.20am. He had previously been active and in good health apart from mild peripheral vascular disease, mild angina (on no regular treatment) and asthma. He took medication for asthma only. Risk factors for stroke included former smoking habit and his mother had died of a stroke aged 56. On examination he had expressive and mild receptive dysphasia, a dense hemiparesis affecting the right face, arm and leg, a right homonymous hemianopia, so was a definite TACI. He was referred to the stroke team at 11.00.

Imaging Studies: The CT brain scan at 1300 hours showed an area of decreased density in the left basal ganglia and white matter lateral to the left lateral ventricle (Figure 4.3.2a). TCD showed no detectable flow in the left ICA, or MCA, and only a very low velocity turbulent bidirectional signal in the region of the A1 segment of the ACA (Figure 4.3.3a). The PCA was patent. The velocity in the right MCA was normal but in the right ACA was increased consistent with supply to both the right and left A2s (Figure 4.3.3b). The findings were consistent with a left ICA occlusion in the neck. Cervical Carotid Duplex examination and MCTT studies were not done prerandomisation in the interest of time. Consent was obtained from his wife, a retired auxilli-

ary nurse from the Department of Neurosurgery.

Angiography : Angiogram of the left common carotid showed an occlusion just below the bifurcation in the bulb. The irregular appearance suggested acute thrombotic occlusion rather than dissection (Figure 4.3.4a). Angiogram of the right common carotid showed patent ICA, MCA, ACA, and filling of the stump of the left A1 and the whole of the left ACA more distally, confirming the TCD findings (Figure 4.3.4b). The treatment infusion was administered at 14.40 hours into the left common carotid artery just below the point of occlusion. The patient suffered no ill effects during the procedure. Repeat films of the left common carotid artery at the end of the infusion period showed no change in the appearance of the occlusion.

Imaging Follow-up: Repeat TCD 12 hours after symptom onset showed slight increase in the turbulent low velocity signal in the region of the left A1, and a very low velocity signal in the region of the proximal left MCA (Figures 4.3.3 c + d). The findings on the right side were unchanged. Angiography at 24 hours after onset showed proximal extension of the left CCA occlusion, a slight improvement in the filling of the left A1 segment of the ACA from the right ICA, and a hint of filling of the left MCA (Figure 4.3.4 c and d). CT brain scan at 24 hours and three days after the stroke showed a well demarcated infarct in the basal ganglia and

white matter lateral to the left lateral ventricle (code 30) with some swelling (code 3) but without haemorrhage. TCD on day three showed a further improvement in the left MCA and A1 segment of the ACA's velocity (Figure 4.3.3 e and f). No further change in the blood velocity pattern occurred up to the last TCD study at three months after the stroke. CT scans at 2 weeks and three months after onset showed little change apart from gradual atrophy of the affected tissue. There was no haemorrhage, even minor, at any time.

Clinical follow up: The patient was discharged to rehabilitation at one month. His neurological state changed little, with no return of power to the right side by three months, but slight improvement in dysphasia. His comprehension at three months was full and he was able to answer yes and no with occasional half sentences. His Oxford Handicap score was five at two weeks and four at three months. His Barthel Index was 14 at two weeks and 39 at three months. At six month follow up he was living at home, cared for by his wife. His Oxford Handicap Score was four and Barthel Index was 32. This patient was randomised to saline.

Patient two: This 29 year old, previously healthy woman on no medication, collapsed at 1400 hours in a street near the WGH, and was brought to the WGH by ambulance. She reached hospital 50 minutes after symptom onset (14.50), and was

assessed by the stroke team at 15.30 hours. She had no known risk factors for stroke.

Clinical features: She had a dense hemiparesis affecting the right side of the face, arm and leg, a right homonymous hemianopia and a complete expressive dysphasia with good comprehension. She had had a headache on the left side of her head for three days prior to admission.

Imaging studies: CT brain scan at 1700 hours showed an ill defined low density consistent with ischaemia in the left basal ganglia, deep hemispheric white matter and adjacent cortex (code 50), with some mass effect (code 2), but no haemorrhage (Figure 4.3.5a). TCD showed reduced velocity in the left MCA (though still clearly detectable), with greatly increased velocity in the left ACA (Figure 4.3.6 a and b), and normal velocities in the right MCA (peak velocity 100cm/s) and ACA. Carotid Duplex showed reduced velocity in the Left CCA and ICA with a low amplitude, bidirectional, high pulsatility waveform which has been described in dissection. An MCTT study was not performed as the daily allocation of isotope had already been used. Consent for angiography was obtained from the patient and her parents.

Angiography: The left MCA was occluded just beyond its origin, with no evidence of dissection in any of the vessels

(Figure 4.3.7 a). The treatment infusion was given at 1940 hours into the distal left ICA, after an attempt to place a microcatheter in the left MCA had failed. Angiogram immediately after the infusion showed partial recanalisation of the left MCA (Figure 4.3.7 b). The patient suffered no ill effects during the infusion.

Imaging Follow-up: TCD at eight hours after onset showed a higher velocity in the left MCA than on admission (though still slightly reduced). At 18 hours the velocity was the same as in the right MCA, although the diastolic flow was higher on the left in keeping with hyperaemia. Repeat angiography at 18 hours showed complete recanalisation of the left MCA (Figure 4.3.7 c). CT brain scan at one and three days after onset showed swelling in the left MCA territory infarct (code 3) with some diffuse increase in density suggestive of petechial haemorrhage (Figure 4.3.5 b and c). The velocity in the left MCA increased to greater than that in the right MCA from day two until day 14 when the velocities became equal (Figure 4.3.6 c + d) and thereafter the left MCA velocity remained normal. This indicated a period of marked hyperaemia in the symptomatic MCA. CT brain scan at two weeks showed some decrease in the swelling and the petechial haemorrhage.

Clinical Follow-up: The patient improved neurologically.

There were no systemic bleeding complications, or problems with the angiogram puncture site. At two weeks she was able to say a few words and her hemianopia had resolved. Her motricity index improved from zero at day three to 23 at two weeks and 151 at three months. Her Oxford Handicap Score was five at two weeks and three at three months. Her Barthel Index was 36 at two weeks and 50 at three months. She returned home (a third floor flat with no lift) at three and a half months. At six month follow up her Oxford Handicap Score was two and her Barthel Index was 50. She continued to live in her third floor flat but had not returned to work. Her speech was slow but otherwise normal. She was randomised to streptokinase.

A transoesophageal echocardiogram has revealed a floppy atrial septum with a small ASD. This was the probable cause of her stroke.

Patient Three : This 68 year old man collapsed at home at 1300 hours, and was found immediately by his wife who called his GP. He arrived at the WGH at 1405 hours. He was assessed by the receiving medical registrar and thought to have only a dense left hemiparesis (ie a LACI), so there was some delay in his assessment by the stroke team.

Clinical features : When seen by Dr Lindley, the patient was noted to have total neglect of his left side, and probably a

left homonymous hemianopia, to be drowsy, agitated, and confused, in addition to a total hemiparesis of the left face, arm and leg (power grade 0/5 all groups on the MRC scale), making the diagnosis a TACI not a LACI. He was an ex smoker, and was hypertensive on admission (BP 180/100) but was not known to be hypertensive previously. He had no other risk factors for cerebrovascular disease. His past history included bleeding gastric erosions in 1981 (he had been told to avoid aspirin), and he consumed around 70 to 80 units of alcohol per week.

Imaging Studies : CT brain scan at 1600 hours was of poor quality because of patient movement, but showed an ill defined area of low density in most of the right hemisphere MCA territory (code 80) consistent with early infarction (Figure 4.3.8). There was no haemorrhage. No velocity signal was detected in the right MCA or ACA by TCD, though a normal velocity signal was detected in the right PCA. The left MCA velocity was normal, and the left ACA was slightly increased. Cervical carotid Duplex ultrasound showed occlusion of the right ICA just above its origin. An MCTT study showed delay in arrival of isotope in, and in transit through the right cerebral hemisphere, confirming the TCD result. Consent for angiography and randomisation in the trial was obtained from the patient's wife.

Angiography : Due to the patient's confusion, and problems with emergency radiology cover, he was not ready for angiography until 20.45 hours (eight hours after onset). The procedure was very difficult due to the patient's agitation. Despite 60 mg of Diazemuls IV and two persons restraining him, he moved continually, and the angiogram films were poor. Only views of the right carotid artery were obtained, confirming an occlusion of the ICA just above its origin (Figure 4.3.9a). The ECA was patent. The treatment infusion was given into the bulb of the right CCA, continual patient movement making it impossible to maintain catheter position in the ICA itself. Angiogram film following the end of the infusion showed that perhaps slightly more of the ICA origin was patent (Figure 4.3.9b). The patient suffered no ill effects from the infusion, and returned to the neurology ward with the right femoral artery sheath in position.

Imaging Follow-up : TCD on the following two days did not show any change in cerebral blood velocities from the admission findings. The CT scanner broke down the day after the angiogram and was out of action for two days, so the first follow-up CT brain scan was obtained 48 hours after the infusion. It showed an infarct of the whole right MCA territory with mass effect causing midline shift but no haemorrhage (Figure 4.3.8b). The angiogram and MCTT studies were not repeated as the patient was still very confused and it

was felt that sedation of the patient would be unethical. The femoral sheath was removed uneventfully 18 hours after the angiogram. There were no bleeding complications.

Clinical Follow-up : The patient remained confused, with fluctuating conscious level. He was noted to be quite hypertensive in the 12 hours following angiography (BP 230/130). This was treated with repeated doses of droperidol and nifedipine which brought his blood pressure down to 160/90. There was no alteration in his hemiparesis, or neglect. Two days after admission he developed atrial fibrillation with a rapid ventricular rate, and had periodic respiration. His cerebral blood velocities varied markedly with the phases of the periodic respiration. Mannitol was given IV for presumed cerebral infarct oedema pending the CT brain scan. Following the CT brain scan he continued to deteriorate, becoming comatose, and died 3.75 days after the stroke.

Post Mortem : This confirmed occlusion (presumed thrombotic) of the right ICA, extending to occlude the right MCA and ACA. The right PCA was patent, as were the left hemisphere arteries. There was a large right MCA territory infarct with swelling causing brain stem compression. There was no haemorrhage in the infarct, but there was a small brainstem haemorrhage thought to be a terminal event secondary to brain stem compression. There was some atheroma in both

carotid bulbs, but no large plaque of atheroma to explain the right ICA occlusion. Examination of the rest of the body showed left ventricular hypertrophy and multiple renal infarcts thought to be the consequence of accelerated phase hypertension. There was no evidence of bleeding anywhere apart from in the brainstem. He was randomised to streptokinase.

Patient four : This previously well 38 year old man developed sudden onset left hemiparesis with dysarthria and neglect at 06.30 hours as he was getting ready to go to work. He was referred to the WGH by his GP and arrived at the Western General Hospital at 08.25. The receiving Medical Registrar referred him to the Neurology Registrar as both Dr Lindley and myself were on holiday.

Clinical findings: On examination he was drowsy but orientated, with neglect of the left side, probable left homonymous hemianopia (difficult to be certain because of the neglect), dense hemiparesis of the left face and arm and mild hemiparesis of the left leg. He had smoked 20 to 40 cigarettes per day for 20 years, but had no other known risk factors for cerebrovascular disease.

Imaging studies : CT brain scan at 10.15 hours showed a low density in the anterior part of the right MCA territory with

sparing of the basal ganglia and minimal mass effect (Figure 4.3.10). TCD showed a reduced velocity in the proximal right MCA, with no signal detected beyond one cm from its origin (Figure 4.3.11a). An MCTT study was not done. The carotid Duplex ultrasound did not show any plaque or stenosis. Verbal consent for angiography and randomisation in the thrombolysis trial was obtained from the patient and his father (by telephone).

Angiography : The angiogram showed an occlusion at the origin of the first main branch of the right MCA (M2 segment) with a small patent branch (Figure 4.3.12a). There was initial difficulty in advancing a microcatheter into the right MCA, so half of the treatment infusion was administered in the distal right ICA. A second attempt to place the microcatheter tip in the occluding thrombus was successful, and the rest of the infusion was given into the thrombus. The arteries distal to the thrombus were patent (Figure 4.3.12b). Repeat angiogram film after the infusion was completed showed that the M2 segment had reoccluded (Figure 4.3.12c). The patient suffered no ill effects during the angiogram and returned to the neurology ward.

Imaging Follow-up : Angiography was repeated the next day (at 30 hours after stroke onset). This showed a tight stenosis at the trifurcation of the right MCA, consistent with

partial recanalisation, with improved filling of the distal branches (Figure 4.3.12d). CT brain scan at 24 hours showed a more clearly defined infarct in the right MCA territory anteriorly and peripherally with some mass effect but no haemorrhage (Figure 4.3.10b). The appearance was similar on day three apart from some minor petechial haemorrhage at the margins of the infarct. CT brain scan at two weeks showed a reduction in mass effect and no haemorrhage.

TCD 24 hours after the infusion showed that the right MCA blood velocity had improved, but was still reduced compared with the left MCA (Figure 4.3.11b). A focal high velocity jet was detected at about 50 mm depth consistent with a focal stenosis of the right MCA. This appearance persisted for the first two weeks after the stroke (Figure 4.3.11 c, d).

Clinical Follow-up : 18 hours after the infusion the patient had a haematemesis, so aspirin was not started. There were no other bleeding complications. On day seven he was alert with persistent neglect of the left, and no change in power of the left face or arm, but the left leg was slightly weaker. By day 14 the power in the left leg had improved to the admission level and there was still no change in the other neurological signs. His Barthel Index was 20 with an Oxford Handicap Score of 5. He was transferred to rehabilitation on day 14. This patient was randomised to streptoki-

nase.

The patient was readmitted to the WGH with a further stroke two months after the first stroke which had lead to randomisation in the streptokinase trial. His conscious level was diminished, he was aphasic and had right arm and leg weakness. Further investigations at that time revealed subacute bacterial endocarditis. At the time of the admission with the first stroke he had microscopic haematuria, but this had been attributed to minor haemorrhage following the streptokinase infusion and not investigated further. There were no other signs of endocarditis at the time, but presumably a cardiac embolus was, in retrospect, the cause of his stroke. At the three month follow up assessment for the streptokinase trial he was severely handicapped - totally dependent, requiring constant attention day and night. It is likely that his recovery from the first stroke was severely impaired by the second stroke so it is difficult to say what benefit, if any, he may have had from the trial treatment.

4.3.4 Discussion

The trial was very labour intensive. The most time consuming and difficult to organise part was the angiography, because that required a nurse, a radiographer (preferably two), a radiologist, and a vacant angiogram room. The angiogram room had to be prepared for each patient and there were several occasions when there were other patients waiting for angiography who had to be deferred. The patients had to give consent not just for the trial treatment, but for angiography also - two risks instead of one - angiography is not pleasant. A minimum amount of cooperation was required from the patient for the angiogram to be successful and worthwhile.

Although only four patients were randomised out of six who had angiography as a prelude to randomisation, with each patient difficulties were encountered which have important implications for the design of acute stroke trials and the management of acute stroke generally. At angiography of the first patient there was debate about where the treatment infusion should be given - whether into the occluded left CCA or into the distal right ICA in the hope that it might reach the left hemisphere and open the left MCA via the left ACA. Intravenous administration would avoid this problem. The patient's hospital management was straightforward with no complications of the stroke or angiogram. His progress in the rehabilitation hospital was slow but uncomplicated.

Sadly the nurse who visited him and his wife to perform the six month follow - up assessment was the first person to visit them since his discharge from rehabilitation two months previously. The patient was in a wheel chair, house-bound because of steps at front and back doors, and totally dependent on his wife. Consequently she was able to leave him only occasionally and with great difficulty for short shopping trips. It is probable that because she was a former nurse and capable person, the community services thought that they would cope well and little home support or assessment had been offered. The trial nurse was able to arrange social work assessment for aids in the home, alert the GP and district nurse to the problem, and put the patient and his wife in contact with a local patient self-help group. This patient, relatively speaking, had made what was regarded as a satisfactory recovery from a severe stroke, but "satisfactory" is a pretty poor substitute for someone who was only 64, and previously active.

The second randomised patient, the 29 year old female, also made uncomplicated progress in hospital after the trial treatment. However the angiography delayed the time to trial treatment by at least an hour, possibly longer, and one wonders if her outcome might have been better had the infusion been administered earlier. Her stroke was eventually attributed to an embolus of cardiac origin from a congenital atrial septal anomaly, which was only detected using

the more sensitive (compared with transthoracic) transoesophageal echocardiography. Occult cardiac defects are being increasingly recognised as a cause of stroke in the young, but the best management is unclear. Should aspirin, or long term anticoagulation be offered? A small regular dose of aspirin is probably not unreasonable, plus simple measures such as not sitting still for long periods of time, good fluid intake, not smoking, careful anticoagulant prophylaxis for surgery and not taking the oral contraceptive pill may be as helpful until more is known about the natural history of these occult cardiac defects.

The third patient was much more difficult to manage because of his confusion and restlessness. He required large doses of benzodiazepines during the angiogram. It was difficult to know how well oxygenated he was as he kept removing the percutaneous pO_2 monitor and oxygen mask. On returning to the ward after the trial infusion, his blood pressure was very high and was lowered pharmacologically, but it is not known if reducing the blood pressure in the acute stages of an ischaemic stroke is advisable or not. If reduced too much there might be further impairment of the cerebral circulation, but in this patient there was concern that the hypertension might predispose to cerebral haemorrhage. Considerably more experience will be required with patients with strokes of all severities to find out what is best in such situations. It is also unclear what should be done about

intravenous fluids and control of respiration. More experience is required.

The fourth patient randomised may have suffered more by being in a trial than had he not been. It was regrettable that he was randomised in the one week of the entire year when both the radiologist and clinician most familiar with the streptokinase trial were on holiday. On the first admission the cause of the stroke was never established, and although there were some warning signs of the probable underlying cause, these were not followed up. The microscopic haematuria was attributed to the trial treatment and ignored, and the fact that he was only 38 and, despite being a very heavy smoker, previously well, did not provoke an exhaustive search for a source of embolus. The high profile of the acute stroke trial may have overshadowed the common sense approach to routine clinical practice. Inclusion of patients in a trial concerned with one aspect of their management should not detract from the other routine aspects.

It was decided at the beginning of the trial, that it would be reasonable for me, but not any other medical staff involved in the trial, to find out whether the treatment infusion was streptokinase or saline, two weeks after administration. It is obviously far too early to draw any broad conclusions from the results, but a few comments are worthwhile.

Firstly there were no significant cerebral haemorrhagic complications, although all the patients who were given streptokinase had deranged blood coagulation, as measured on a peripheral arterial sample taken four hours after the trial infusion, but not after saline. One patient (No. 4) had a systemic bleeding complication.

Three patients received streptokinase and one saline placebo. One patient died (SK), two made poor recoveries (one SK, one placebo), and one made a good recovery and returned to independent living (SK). One patient recanalised the occluded MCA quickly (SK), one showed partial recanalisation of the occluded MCA by 24 hours (SK), one showed minimal evidence of recanalisation of the MCA above an occluded CCA by 24 hours (placebo), and the other had no evidence of recanalisation from an ICA occlusion at all (SK).

After my departure from the WGH, the pilot thrombolysis trial stopped because of lack of a dedicated member of staff. Hopefully the WGH will be able to continue similar work by joining one of the intravenous multicentre randomised controlled thrombolysis trials now underway, such as the Multicentre Acute Stroke Trial - Italy.

Summary of Chapter Three

1. Patients considered for the Thrombolysis Trial and reasons for exclusion are described to illustrate some of the problems encountered.
2. Publicity measures to promote the trial are described.
3. Each of the four patients randomised in the Thrombolysis Trial are described in detail.
4. The pilot trial terminated after one year because I left the WGH, but it is hoped that the WGH will continue similar work by joining one of the multicentre randomised controlled trials of thrombolysis now being set up.

Table 4.3.1 Patients who were actively considered for the Pilot Intraarterial Thrombolysis Trial, and reason for exclusion where appropriate - February 1991 to December 1991. All times are from stroke onset.

No.	Age	Time to WGH	Time to "Stroke Team"	D ₁	Time to X-ray	D ₂	Reason for Exclusion	Outcome at 3 months
1	59	5.5	7.8	2.3	8.2	0.4	infarct visible	in hosp.
2	80	1.5	2.5	1.0	3.0	0.5	haemorrhage	LTC
3	82	3.0	3.0	0.0	3.75	0.75	infarct visible	rehab
4	64	4.9	6.5	1.4	7.25	0.75	infarct visible	rehab
5	66	0.9	3.0	2.1	4.5	1.5	unscannable	died
6	70	in WGH	0.5	0.5	4.0	3.5	SK given for MI	died
7	66	4.5	7.5	3.0	8.5	1.0	infarct visible	LTC
8	84	6.5	7.5	1.0	7.75	0.25	infarct visible	LTC
9	67	in WGH	1.0	1.0	1.75	0.75	rapid recovery	LTC
10	64	1.0	1.5	0.5	3.0	1.5	R	rehab
11	84	4.0	6.0	2.0	NR	NR	consent unobtainable	in hosp.
12	29	0.75	1.5	0.75	2.0	0.5	R	home
13	79	8.5	24.0	15.5	NR	NR	not referred	dead
14	84	in WGH	0.75	0.75	2.0	1.25	IST	in hosp.
15	55	4.0	4.0	0.0	4.0	0.0	lacunar infarct	home
16	61	2.5	3.0	0.5	4.0	1.0	aneurysm	home
17	68	1.0	3.0	2.0	4.0	1.0	R	died
18	78	5.0	6.0	1.0	NR	NR	"stroke team busy"	in hosp.
19	72	1.0	10.0	9.0	14.0	NR	time delay	died
20	38	2.0	2.5	0.5	3.75	1.25	R	rehab
21	70	2.0	2.5	0.5	3.0	0.5	pt. declined trial after angio	home

WGH = Western General Hospital

NR = not relevant

D₁ = time delay in hours between arrival in hospital and referral to "Stroke Team"

D₂ = time delay in hours between referral to "Stroke Team" and CT brain scan

IST = patient randomised into a concurrent trial, the International Stroke Trial

R = randomised in the thrombolysis trial

LTC = patient in long term care unable to return home



Figure 4.3.1 A The "expectant" policy of stroke management.
? "Top Gun" approach?



Figure 4.3.1 B "Minimalist" management.

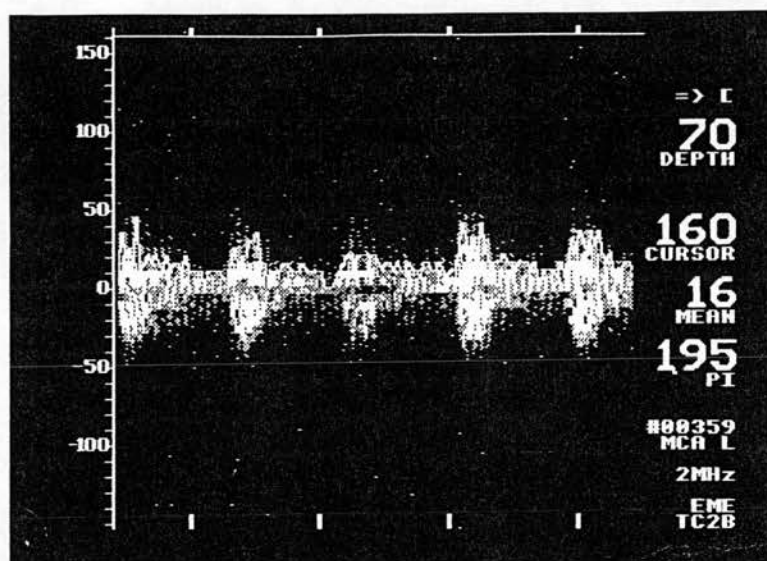
Figure 4.3.2a Patient One : CT brain scan at 2.5 hours after onset of acute ischaemic stroke prior to randomisation. There was ill defined low density in the left parietal white matter and basal ganglia.



Figure 4.3.2b Patient One : CT brain scan at three days after stroke onset showing a large subcortical infarct involving the left basal ganglia and deep hemispheric white matter. No haemorrhage.



Figure 4.3.3 Patient One : a,b. Transcranial Doppler findings at 2.5 hours after onset of acute ischaemic stroke.
a) Left ACA (symptomatic side) - only a low velocity turbulent bidirectional flow signal was detected on the symptomatic side. No MCA signal detected. The signal shown was in the region of the ACA.



b) Right MCA and ACA (asymptomatic side). The signal above the baseline was the ACA, and was increased above the expected normal level in keeping with supply to both A2 segments.

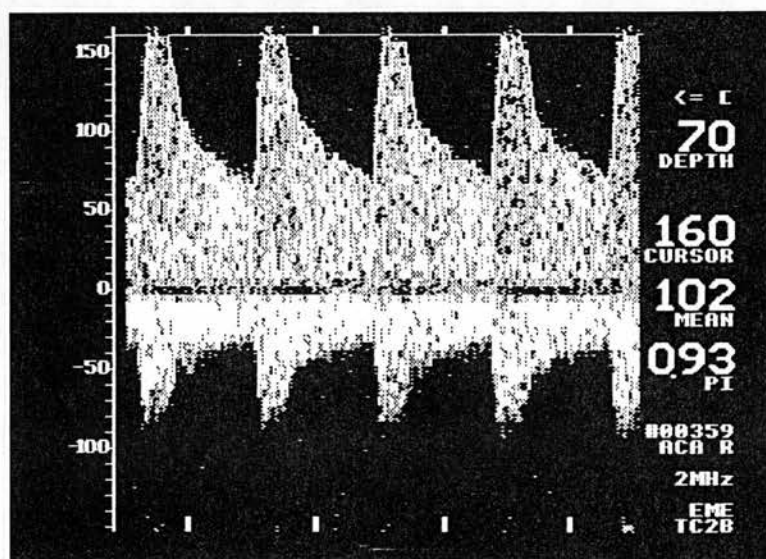
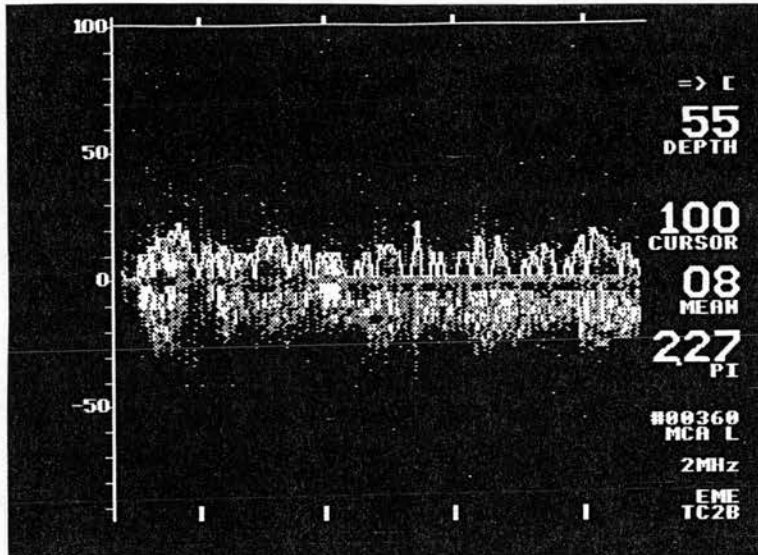


Figure 4.3.3 Patient One continued : c,d. Transcranial Doppler at twelve hours after symptom onset.

c) Left - there was a very low velocity turbulent signal detectable in the MCA main stem, compatible with minimal blood flow into it.



d) Left - the signal in the region of the ACA had increased, in keeping with marginally better flow to the left hemisphere.

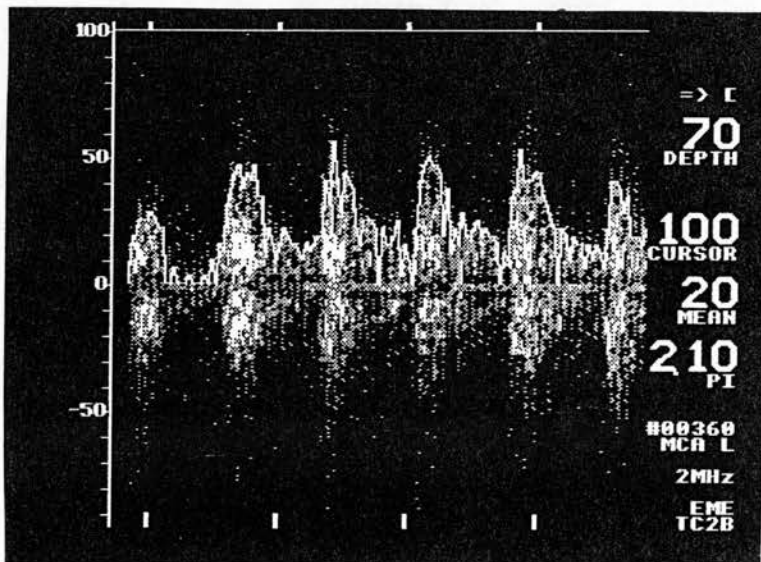
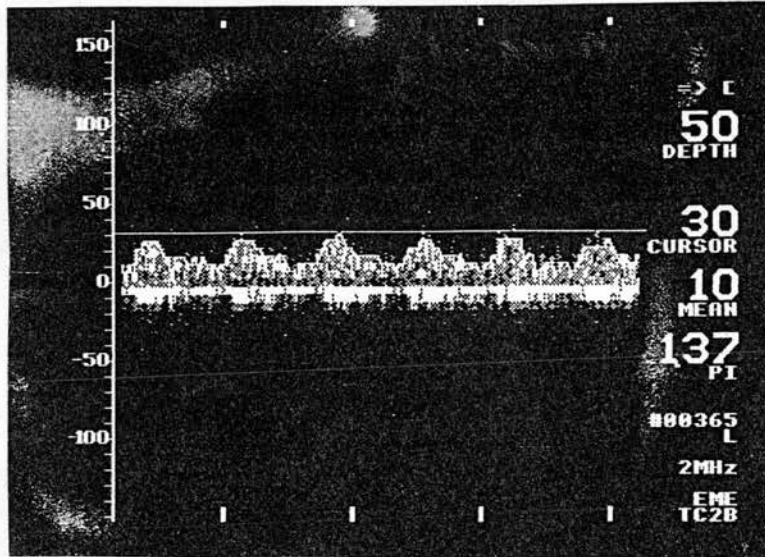


Figure 4.3.3 Patient One continued : e,f. Transcranial Doppler three days after acute stroke onset.

e) Left MCA - a much more distinct signal was detectable in the left MCA. It was still considerably reduced from normal, but was definitely present.



f) Left ACA - the signal in the ACA had increased further and was reversed, in keeping with persistent occlusion of the left ICA and collateral supply from the right ICA.

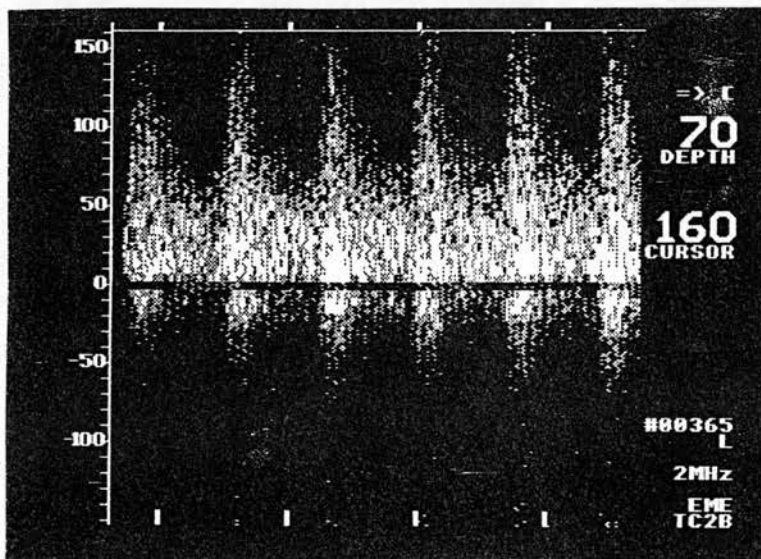


Figure 4.3.4 Patient One : a,b. Angiogram at three hours after stroke onset.

a) Left carotid injection - the CCA was occluded in the bulb.

b) Right carotid injection - the ICA was patent and filled the right intracranial arteries normally. The left A1 was just visible but there was no flow back into the left MCA.

a)

b)

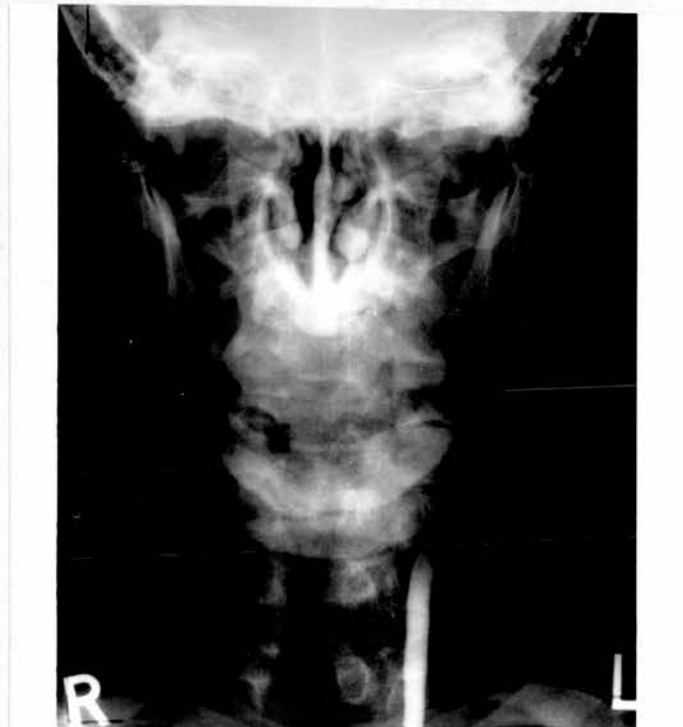


Figure 4.3.4 Patient One : c,d. Angiography 18 hours after symptom onset.

c) Left CCA - the occlusion had moved more proximally.

d) Right CCA injection - there was marginally better filling of the left ACA, and a very faint outline of the left MCA suggesting slight recanalisation.

c)



d)



Figure 4.3.5 continued Patient Two : b. CT brain scan at three days after symptom onset. The low density area in the left basal ganglia and parietal cortex had become more distinct. Swelling in the infarct had increased but there was no midline shift. The margins of the infarct were a little hyperdense suggesting that there may have been some mild petechial haemorrhage.

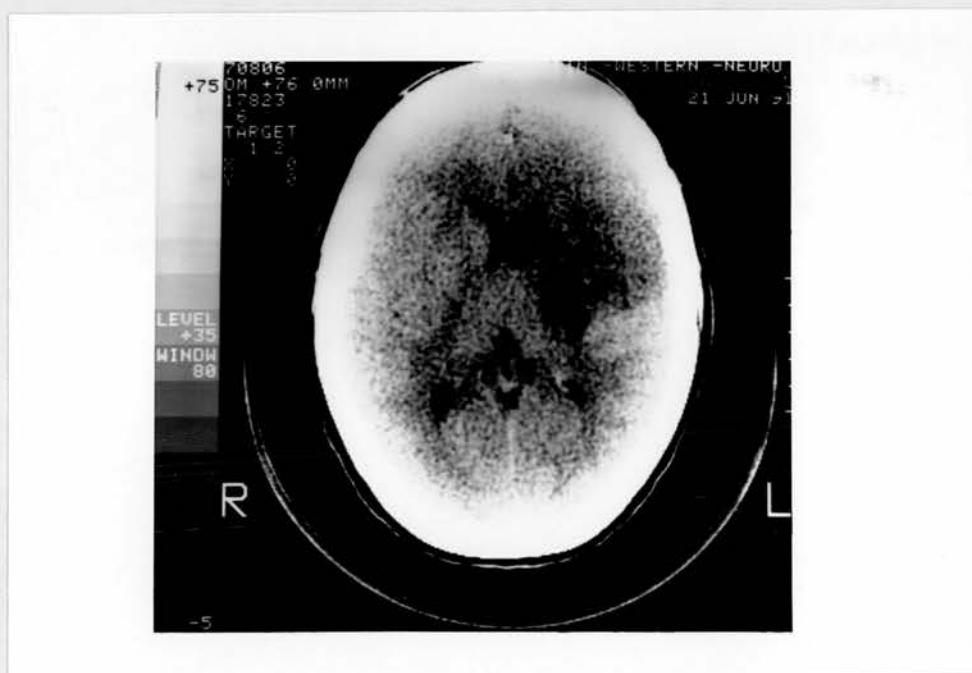


Figure 4.3.5 continued. Patient Two : c. CT brain scan at two weeks after symptom onset. The swelling had resolved but there was still low density in the left basal ganglia. However the infarct extent was much more difficult to see - an example of the "fogging" effect.

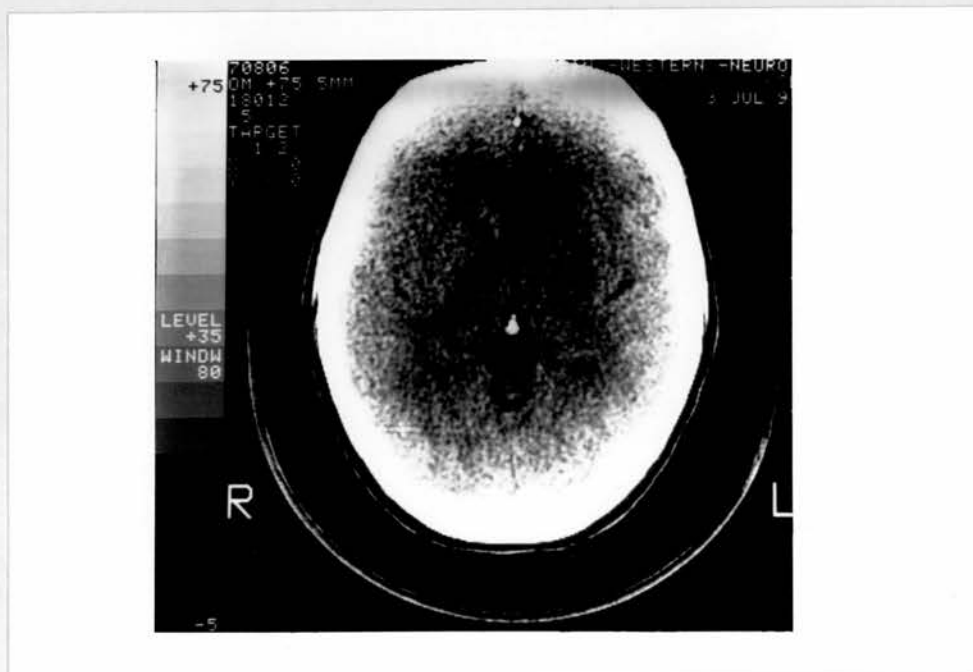
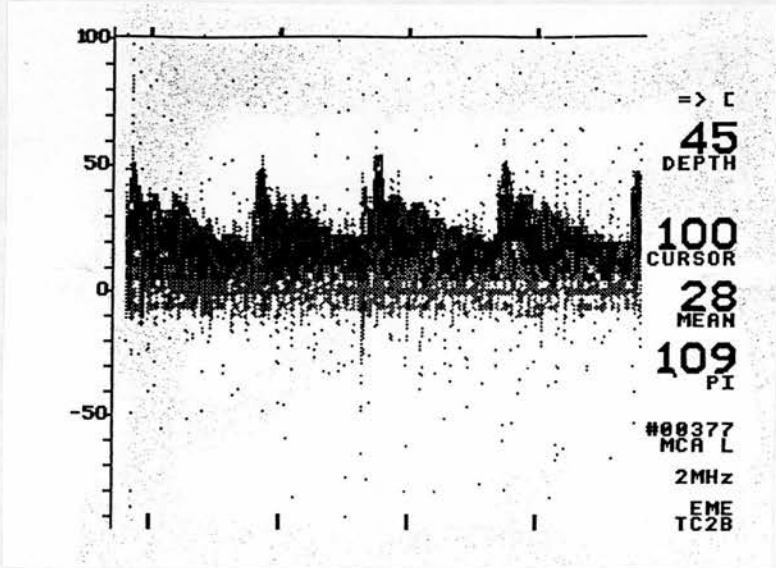


Figure 4.3.6 Patient Two : a,b. Transcranial Doppler within three hours of symptom onset.
a) Left MCA (symptomatic side) - reduced but still detect-able signal in keeping with an MCA main stem or first branch occlusion. The right MCA mean blood velocity at the same depth (45 mm) was 78cm/sec.



b) Left ACA - greatly increased velocity in keeping with collateral supply to the peripheral MCA territory.

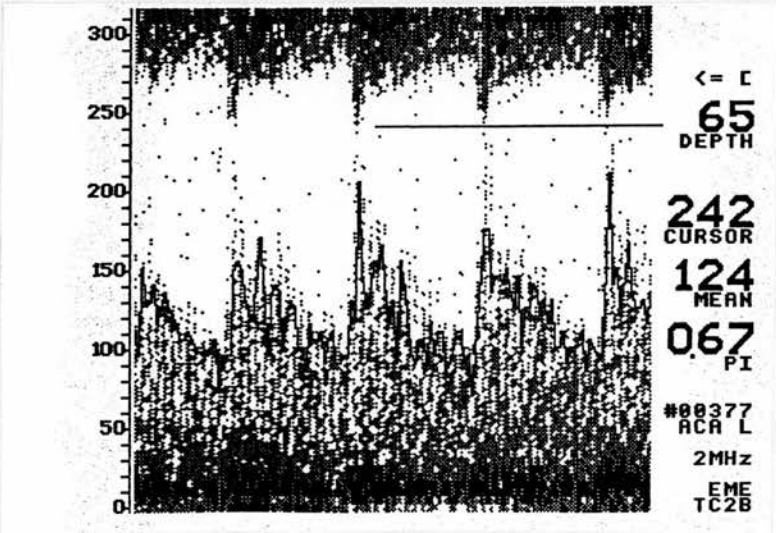
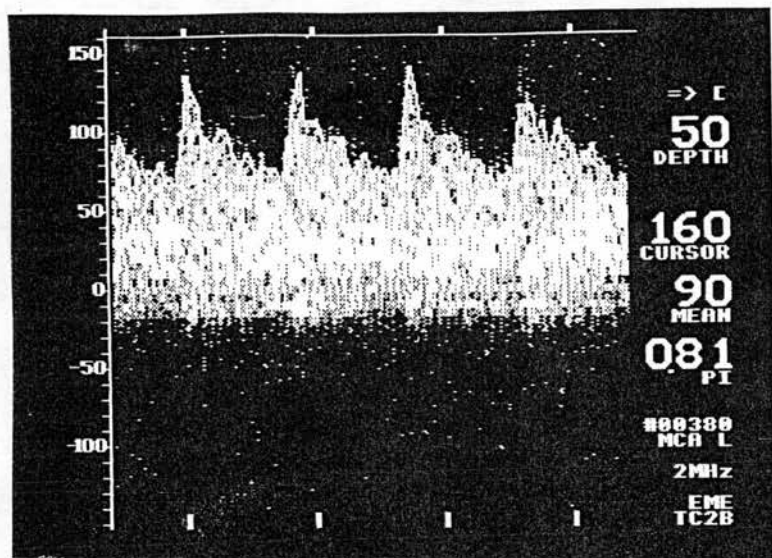


Figure 4.3.6 continued. Patient Two : c,d. Transcranial Doppler three days after symptom onset.

c) Left MCA - the mean velocity was increased (upper limit of normal for this age group is 86) and the pulsatility index (PI) was low in keeping with hyperaemia.



d) Right MCA for comparison - the velocity was normal.

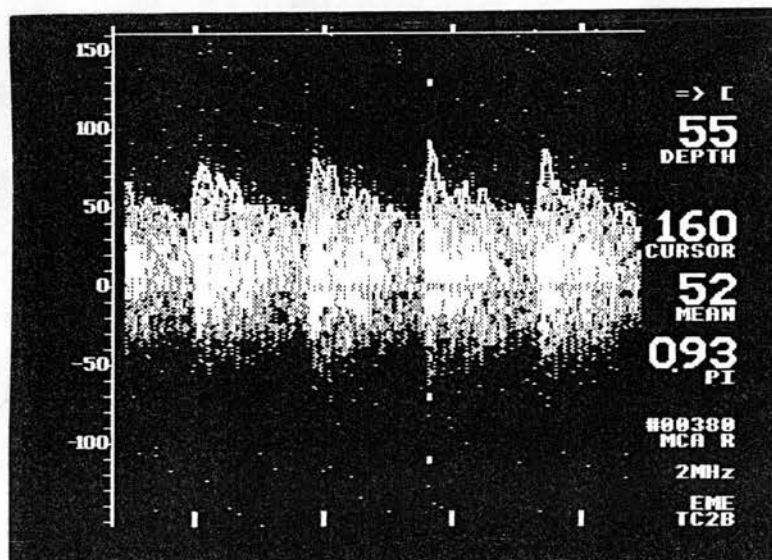


Figure 4.3.7 Patient Two : a,b,c. Cerebral angiography pre and post treatment infusion.

a) Left carotid injection within four hours of symptom onset- the left MCA was occluded in the main stem. There was no evidence of dissection of the internal carotid artery.

b) Left carotid injection - immediately after the treatment infusion - the left MCA had partially recanalised.



c) Left carotid injection 18 hours after symptom onset- the left MCA had completely recanalised.



Figure 4.3.8 Patient Three : a. CT brain scan at three hours after symptom onset. The image quality was degraded by movement but an area of low density was visible in the right MCA territory with some mass effect.

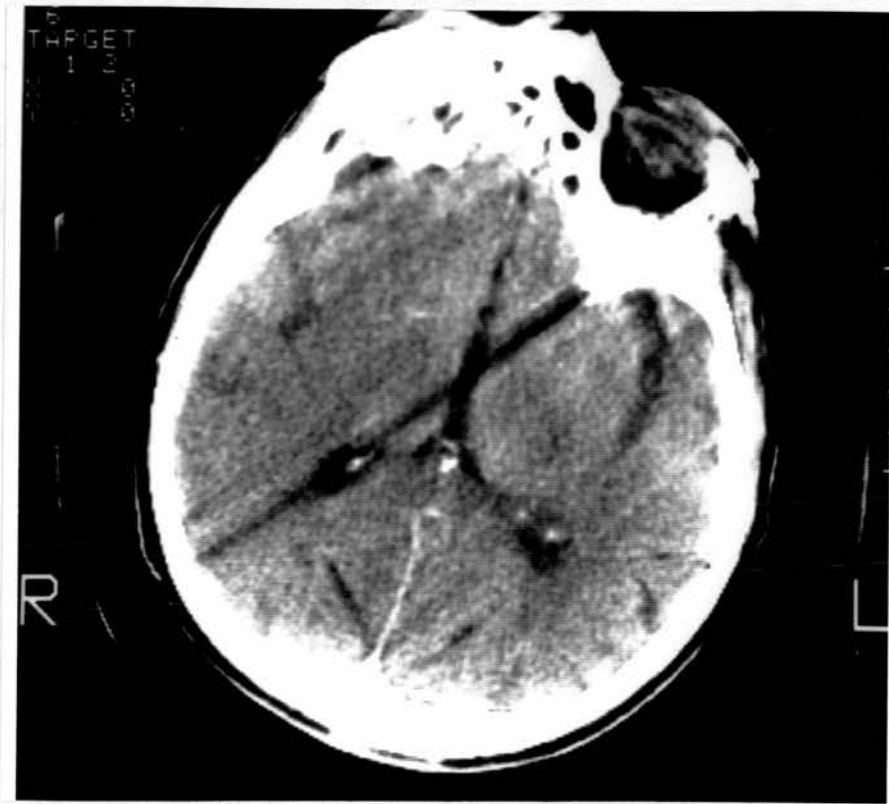


Figure 4.3.8 Patient Three : b. CT brain scan at two days after stroke onset. There was infarction of the whole MCA and part of the PCA and ACA territories with massive swelling, midline shift and effacement of the basal cisterns. No haemorrhage.



Figure 4.3.9 Patient Three : Angiography at eight hours after symptom onset.

- a) Right carotid injection - the right ICA is occluded just above its origin. The outline of the bulb appears smooth without atheromatous plaque.
- b) Right carotid injection - immediately after the treatment infusion - no change in the appearance of the occlusion.

a)

b)

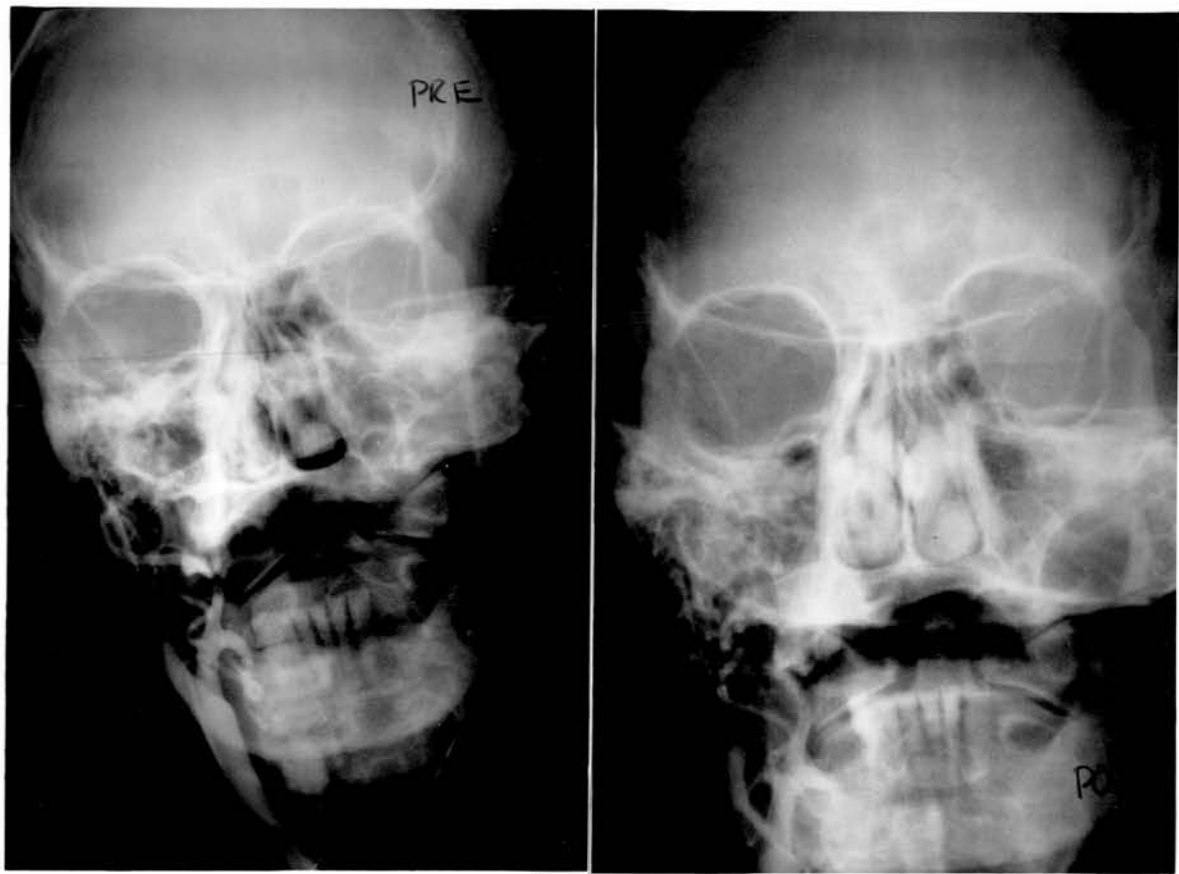


Figure 4.3.10 Patient Four : a. CT brain scan two hours after onset of symptoms. Ill defined low density is visible in the anterior part of the right MCA territory consistent with infarction.

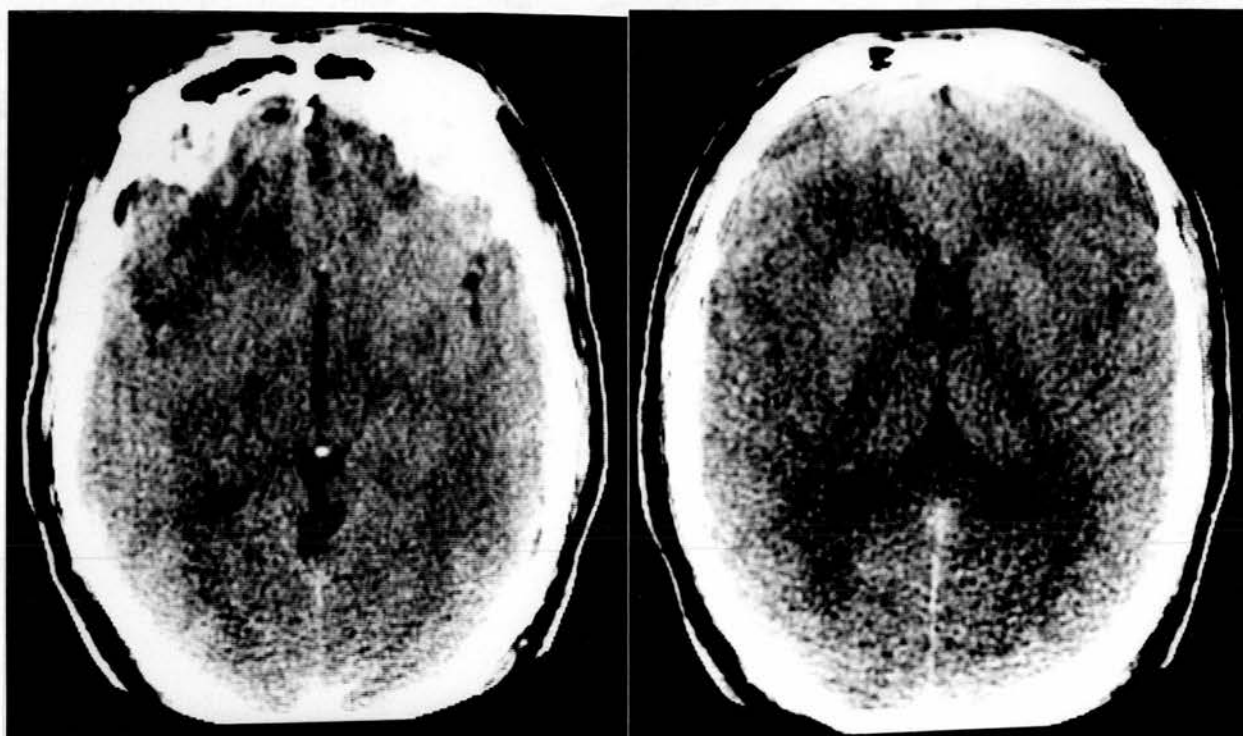


Figure 4.3.10 Patient Four : b. CT brain scan three days after symptom onset. The right MCA infarct was more clearly visible and shows some mass effect and increase in density of the tissue at the margins of the infarct suggestive of minor petechial haemorrhage.

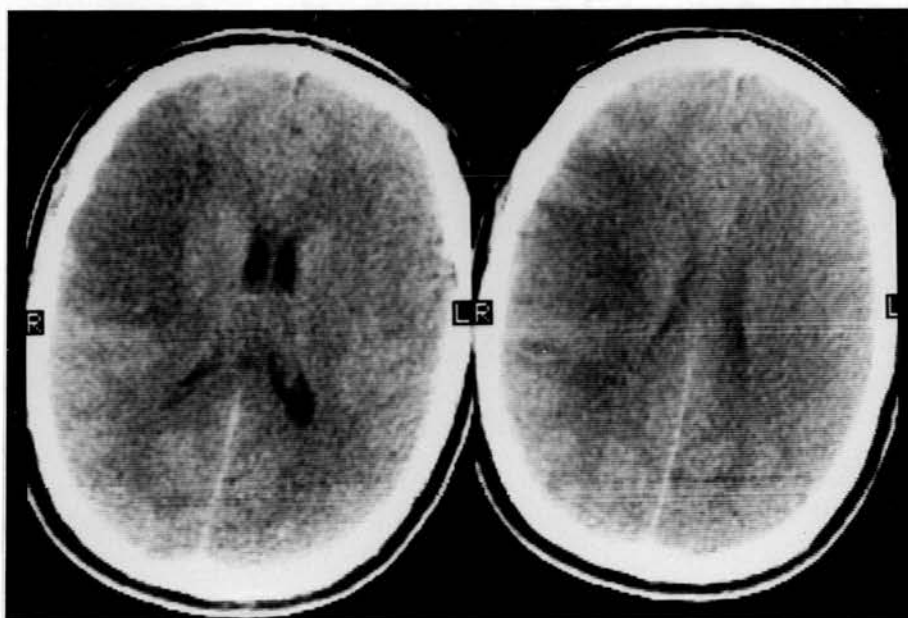
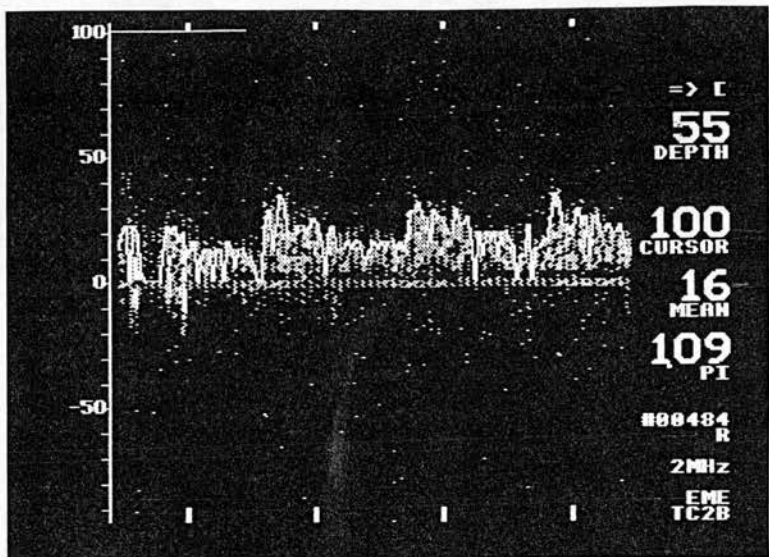


Figure 4.3.11 Patient Four : Transcranial Doppler.

a) Right MCA three hours after symptom onset - the velocity was markedly reduced. The mean blood velocity in the left MCA was 60 cm/sec.



b) Right MCA 24 hours after treatment infusion - the velocity in the MCA had improved but was still reduced below normal.

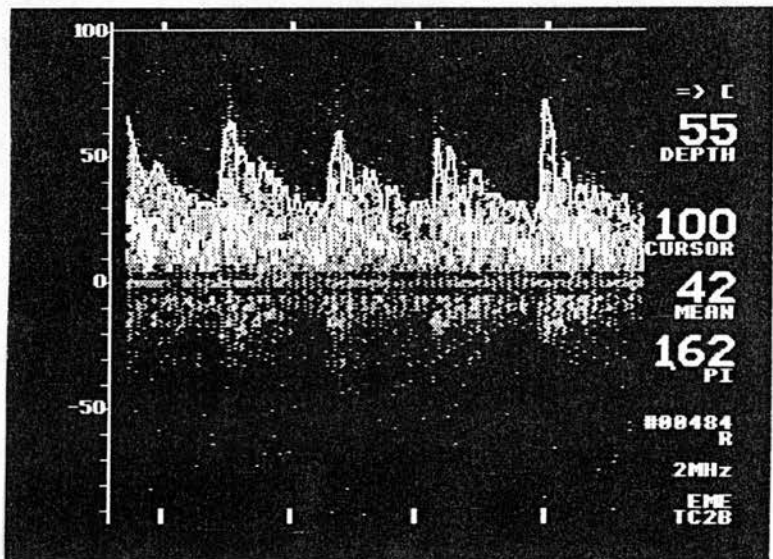
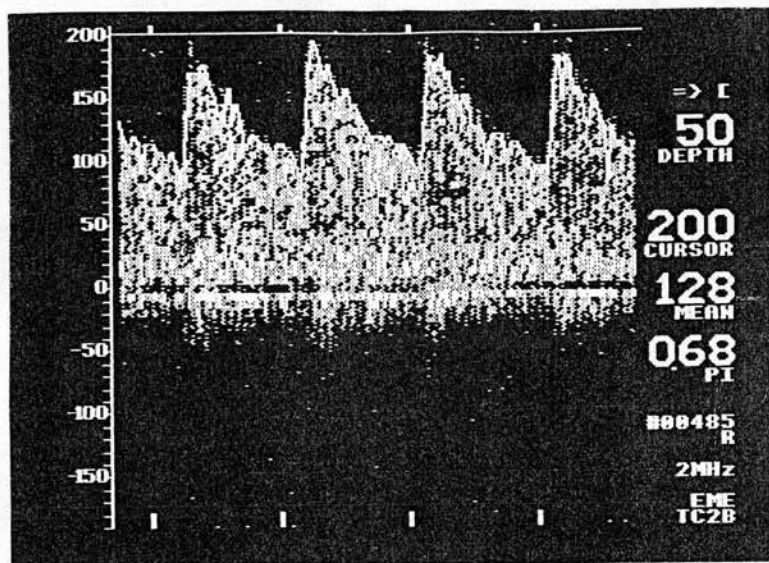


Figure 4.3.11 Patient Four continued : Transcranial Doppler
 c) Eight days after symptom onset : the right MCA - the mean velocity was increased at a depth of 50 mm only, consistent with a persistent focal stenosis at the MCA trifurcation.



d) Left MCA at 50 mm depth - asymptomatic side for comparison.

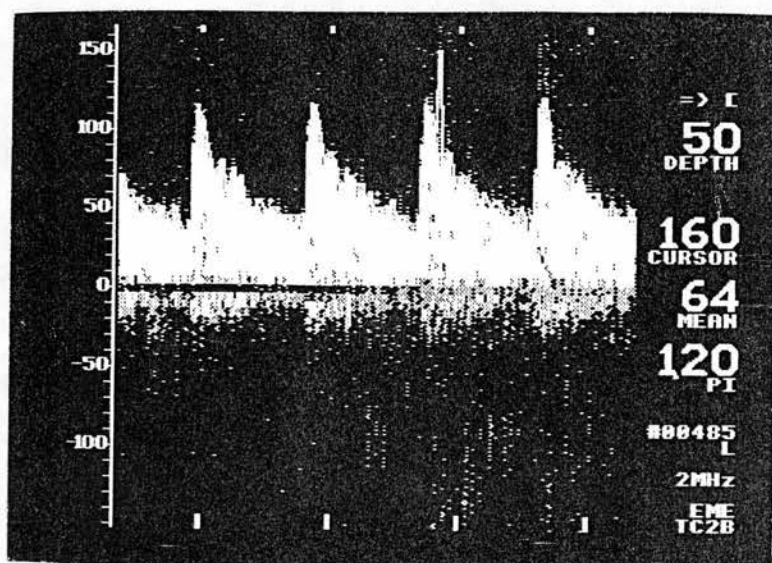


Figure 4.3.12 Patient Four : Cerebral Angiography.

a) Right side, three hours after symptom onset through a microcatheter placed in the MCA - there was an occlusion at the trifurcation of the MCA with only a small temporal branch remaining patent.



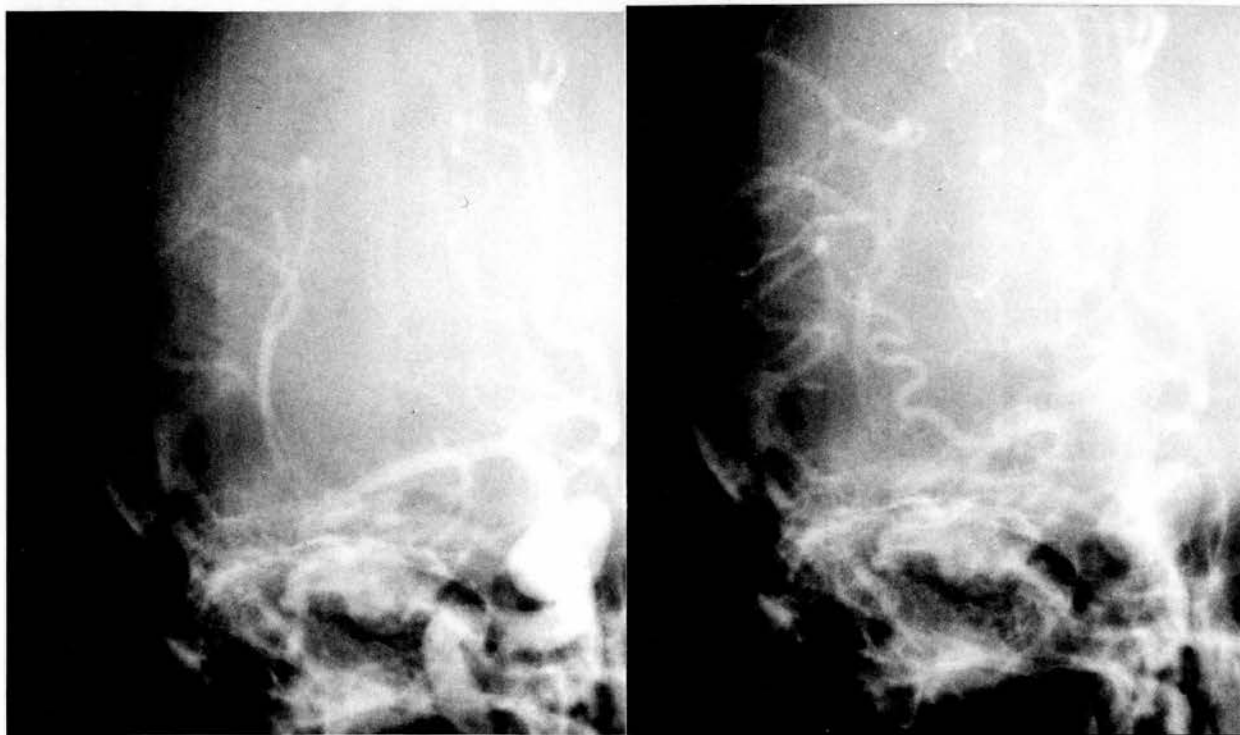
b) Right MCA with the tip of the microcatheter embedded in the thrombus after the first part of treatment infusion - the MCA distal to the thrombus is patent.



Figure 4.3.12 Patient Four continued : Cerebral Angiography
c) Right MCA through the microcatheter in the distal ICA at the end of the treatment infusion - the MCA had reoccluded at the same point.



d) Right MCA 30 hours after stroke onset - early and late phases of the angiogram series showed partial recanalisation of the MCA with a persistent stenosis at the MCA trifurcation, but improved distal filling of the MCA branches



Part Four

Chapter Four

Thrombolysis in Acute Ischaemic Stroke - Does it work?

**The Intraarterial Thrombolysis Pilot Trial and Acute Stroke
Treatment Trials in General.**

Discussion.

4.4.1 Lessons from the pilot trial

**4.4.2 Future trials of thrombolysis in acute ischaemic
stroke**

4.4.1 Lessons from the pilot trial

This small pilot study, though unsuccessful in reaching its target or any meaningful conclusion, was nevertheless useful in that it highlighted many aspects of acute stroke management which are poorly dealt with at present. It also gave useful insights to aid the design of future stroke trials. Some of the important messages have already been discussed in Chapter Three, but other points will be covered here.

Obtaining consent from patients or their relatives for this complex trial was not difficult in spite of the angiography and potential risk of cerebral haemorrhage. Most patients seemed to be aware that there was little treatment that could be offered for the acute stroke, and knew that "clot dissolving" drugs work in myocardial infarction. They were prepared to accept the unquantified risk of cerebral haemorrhage for the possibility of benefit from streptokinase. It had been anticipated that obtaining consent would be one of the most difficult hurdles to overcome, but it was not. Future acute stroke trials with less daunting protocols should have little problem with consent. Consent must be humane and the explanation of the nature of the trial simple. The patient and their relatives are frightened and confused and not able to take in complicated explanations. There must be ready access at all times to informed staff

who can answer questions.

Randomisation in a trial should not detract from or distract the medical staff from the routine medical care of the patient. Patients should be managed appropriately whether they are in a trial or not. Acute stroke trials are likely to increase so care must be taken not to forget routine medical practice.

Patients can get to hospital quickly after an acute ischaemic stroke, but once they reach hospital there are numerous time delays which interfere with their rapid investigation and implementation of therapeutic manoeuvres. Patients seem to get to hospital more quickly if they go direct to the Casualty Department without involving their General Practitioner. Many of the delays in hospital seem to result from the perception that there is little that can be offered therapeutically to stroke patients. However that does not mean the same thing as total neglect of even basic nursing care and medical practice. Patients may wait several hours in the Casualty Department waiting to be seen by the receiving doctor and for a bed to be made available in a ward, meanwhile they develop bed sores, aspirate, become hypoxic, have arrhythmias or blood pressure variations which further impede their cerebral circulation, etc. There is probably quite a lot of benefit for stroke patients just in improving attention to simple measures of medical care, before any pharmacological treatment becomes available. Some

of this is speculative, but so little is known about "secondary insults" after acute ischaemic stroke. Proper medical and nursing care must go hand in hand with any pharmacological measures, as in the treatment of any other common medical condition.

Patients with large acute ischaemic strokes are difficult to manage, and if therapeutic intervention is to succeed in the future, then more attention will need to be given to managing intercurrent events such as marked hypertension or hypotension, oxygenation, fluid balance, and probably factors such as blood coagulability, maintaining regular respiration, and posture to name a few. Monitoring will be required to detect such abnormalities, possibly more than could be easily provided on a General Medical ward with current staffing levels. Therefore Acute Stroke Units are probably essential to allow proper administration of drugs, monitoring and treatment of events in the acute phase of the stroke which might adversely affect outcome.³²⁵ In an individual patient each of these factors may have a minor effect on outcome, but when added together and when applied to the total population of stroke patients, even avoidance of minor insults may produce significant and worthwhile benefits in outcome.

Sedation of acute stroke patients will probably also be necessary to allow proper management. Neuroanaesthetic techniques used to manage acute head injuries, subarachnoid

haemorrhage, and primary intracerebral haemorrhage may be appropriate for acute ischaemic stroke also.

4.4.2 Future trials of thrombolysis in acute ischaemic stroke

Future trials must be as simple as possible to encourage the cooperation of already busy medical staff who will see a treatment for stroke as extra work. There are several stages in the admission and investigation of stroke patients at each of which further delays can occur so that the final time when a therapeutic measure can be offered gets further and further postponed. In acute ischaemic stroke, it is likely that if any of the promising acute treatments are to work, that they must be administered with minimum time delay. Therefore the admission and investigation procedure for stroke patients should be kept as simple and brief as possible. Trials of promising treatment for stroke should reflect this. Hospital practice is complicated enough already without introducing complex trial protocols.

The intraarterial thrombolysis pilot trial was necessarily complicated because of the question it was addressing. It was not intended that cerebral angiography or routine non-invasive imaging tests, apart from a CT scan, should be used in the majority of stroke patients. For acute stroke trials to succeed in general hospitals where most

stroke patients are admitted, the protocols must be simple - the patients must be easy to identify, the entry criteria broad without too many exclusions, the investigations minimal, and the follow up done by staff outside the hospital. Most acute stroke patients are first seen by junior medical staff on admission to hospital. They are inexperienced, and may be overwhelmed by complex neurology. Even making the diagnosis of a stroke may be difficult.

The moral dilemma concerning the treatment of elderly patients is very important in acute stroke. All our trial patients were under 70 years of age, and there is a general reluctance to treat elderly patients with a severely disabling disease, although attitudes to care of the elderly change constantly. The large thrombolysis in myocardial infarction trials have shown that the elderly have the most to gain from thrombolytic treatment, and the same may be true of treatments for acute ischaemic stroke.^{360,370,371} A better understanding of the benefits (or otherwise) of treating elderly stroke patients is far in the distant future. This cannot really be assessed until a successful treatment is found. Only then will we be able to say if a treatment which improves mortality is worthwhile, or if it just increases the number of heavily dependant elderly patients by keeping alive those who might otherwise have died.

Acute stroke is a difficult disease to treat. Deci-

sions must be made quickly, so trials must be as simple as possible. The thrombolysis trial was complicated, but the treatment procedure was not intended to be adopted into day to day practice. If thrombolysis does work, then it will need to be given by the simplest quickest route possible after the minimum number of investigations. CT brain scan and intravenous administration would be the most adaptable to general use.

Acute ischaemic stroke is a distressing illness : to the patient, the patient's family and friends, and to the medical and nursing staff caring for the patient. Decisions about how much resuscitative and supportive care to offer a patient who has suffered a severe stroke are very difficult to make, and each case must be judged individually.³⁹¹ These decisions may become even more difficult when a proven treatment becomes available, and it will take very large trials to find the true risk/benefit ratio for all types and severities of stroke. For example, a treatment which reduces death or disability by 25% might reduce the number of patients who die following a TACI stroke, and increase the number of independant survivors, but paradoxically might also increase the number of dependant survivors. The same treatment might decrease the mortality and increase the number of independant survivors following a POCI, PACI or LACI stroke, but only decrease slightly if at all the number of dependant survivors. The moral dilemmas posed by these

possibilities are a long way in the future. We have to find a treatment for acute ischaemic stroke first.

Since I began thinking about thrombolysis in 1988, there has been a general groundswell of interest in thrombolysis in acute ischaemic stroke, and a trend away from dose range finding studies to randomised controlled trials, with improved methodology. There are now five multicentre randomised controlled trials of thrombolysis in acute ischaemic stroke underway or just about to start :

- the Multicentre Acute Stroke Trial -Italy (SK/SK+aspirin/aspirin/control - 6 hours),
- the Australian Streptokinase Trial (SK/Placebo- 4 hours),
- the NIH tPA Trial (tPA/Placebo 180 minutes),
- the Multicentre Acute Stroke Trial - France (SK/Placebo - 6 hours),
- the European Cooperative Acute Stroke Study (tPA/placebo)

In addition there are three cooperative projects underway to collect and review the results of future randomised controlled trials to try to derive results and disseminate important information more quickly. These are :

- the Thrombolysis in Acute Stroke Pooling Project based in Lyon in France,
- the Acute Stroke Trials Registry based in Ottawa, Canada,
- the Cochrane Collaboration Stroke Review Group.

All of this will provide some information, but I suspect that even larger trials will be needed, akin to the myocar-

dial infarction trials, before the true risk/benefit ratios of thrombolysis - different drugs, ages, time after onset, doses, combination with other drugs - are established conclusively.

The Edinburgh Thrombolysis Trial was a small drop in the ocean of work needed to establish whether thrombolysis might work. If it has served to raise consciousness, counteract complacency and encourage a rethink of some of the established ideas about cerebrovascular disease, then it has been worthwhile.

Summary of Part Four

1. A review of published data on the use of thrombolysis in acute ischaemic stroke shows that most of the trials of thrombolysis used methodology which does not allow any assessment of its value in acute ischaemic stroke.
2. Six randomised controlled trials have been published, and overview analysis of these does show some evidence of benefit, sufficient to encourage large randomised trials with sound methodology.
3. The background to the Intraarterial Pilot Thrombolysis Trial has been described.
4. Each patient randomised to date in the Pilot Thrombolysis Trial is described in detail.
5. General points regarding the management of acute stroke patients, and their relevance to acute stroke treatment trials, highlighted by the experience with the patients randomised in the thrombolysis pilot trial are discussed.
6. There are now five multicentre randomised controlled trials of thrombolysis in acute ischaemic stroke underway around the world, and a Fibrinolysis Therapy Trialists' Collaboration to analyse and disseminate quickly the results of trial overviews set up.
7. Thrombolysis in acute ischaemic stroke is now on a methodologically much sounder footing.

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Appendix 1 : Definitions.

a.Stroke

Rapidly developing clinical symptoms and/or signs of focal and at times global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. (after Hatano³⁹³ from the WHO, and also used in the Oxfordshire Community Stroke Project²⁵).

b.Cerebral Ischaemia

Rapidly developing clinical symptoms and/or signs of focal and at times global (patients in coma) loss of cerebral function due to sudden interruption of the blood supply to the area of brain subtending those functions. The duration of interruption of the blood supply will determine whether the brain tissue actually dies (infarction) or recovers.

Appendix 2: The Oxfordshire Community Stroke Project (OCSP) Clinical Classification of Acute Ischaemic Stroke.

The OCSP classifies all acute stroke patients into one of four clinical syndromes (Bamford et al 1991)²⁵:

Total Anterior Circulation Syndrome (TACS)

Partial Anterior Circulation Syndrome (PACS)

Posterior Circulation Syndrome (POCS)

Lacunar Syndrome (LACS)

This is a simple classification to apply and most patients fit fairly easily into one of the categories. It is intended for the classification of cerebral ischaemia but can be applied to cerebral haemorrhage also. When the lesion is known to be an infarct then "I" for "infarction" can be substituted for the "S" for "syndrome". The clinical features of each of the syndromes are as follows:

1) Total Anterior Circulation Syndrome (TACS) : Patients must have all three of :

a) new higher cerebral dysfunction (eg dysphasia, dysgraphia, visuospatial disorder);

b) homonymous visual field defect; and

c) ipsilateral motor and/or sensory deficit of at least two areas of the face, arm and leg.

If the conscious level is impaired and formal testing of higher cerebral function or the visual fields was not possible, a deficit is assumed to be present.

2) Partial Anterior Circulation Syndrome (PACS) : Patients presenting with :

only two of the three components of the TACS;

or with higher cerebral dysfunction alone;

or with a motor/sensory deficit more restricted than those classified as a LACS (eg confined to one limb, or to face and hand but not to the whole arm).

3) Posterior Circulation Syndrome (POCS) : Patients presenting with any of the following;

ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit;

bilateral motor and/or sensory deficit;

disorder of conjugate eye movements;

cerebellar dysfunction without ipsilateral long tract deficit (ie ataxic hemiparesis);

or isolated homonymous visual field defect.

4) Lacunar Syndrome (LACS) : Patients presenting with :

pure motor stroke, or

pure sensory stroke, or

sensori-motor stroke, or

ataxic hemiparesis.

Although patients with faciobrachial and brachiorural involvement are included, those with more restricted deficits are not.

Appendix 3 : Coding for cerebral infarcts as seen on CT brain scans.

Site and extent of lesion: Refers only to recent lesions likely to be symptomatic.

Infarcts in the MCA territory :

- 00 normal (includes age-appropriate atrophy, + generalised periventricular lucency)
- 10 small cortical infarct in the MCA territory
- 20 infarct involving most of the basal ganglia (larger than 1.5 cm diameter - striatocapsular)
- 30 infarct in the white matter lateral to the lateral ventricle (larger than 1.5 cm in diameter - also striatocapsular but nearer to the vertex)
- 40 infarct of the front half of the peripheral MCA territory excluding the basal ganglia
- 50 infarct of the posterior half of the peripheral MCA territory excluding the basal ganglia
- 60 infarct of the whole of the peripheral MCA territory not including the basal ganglia
- 70 infarct of the whole of the peripheral MCA territory plus part of the basal ganglia
- 80 infarct of the entire MCA territory

Infarcts outside the MCA territory:

- 01 infarct of part or all of the PCA territory
- 02 infarct of the ACA territory
- 03 borderzone infarct (MCA/PCA, or MCA/ACA)
- 04 brainstem or posterior fossa infarct
- 05 lacunar infarct (small subcortical infarct less than 1.5 cm diameter)

Other :

- 90 primary intracerebral haemorrhage - site indicated by code as for infarcts

Infarcts at more than one site were indicated by combining the codes, for example "11" = small cortical MCA infarct plus PCA infarct.

Definition of the amount of swelling of the infarct

- 0 no swelling
- 1 effacement of the sulci overlying the infarct
- 2 1 + slight compression of the ipsilateral lateral ventricle
- 3 complete effacement of the ipsilateral lateral ventricle
- 4 effacement of the ipsilateral lateral and third ventricles
- 5 4 + shift of the midline structures away from the infarcted side
- 6 5 + effacement of the basal cisterns

Definition of the amount of haemorrhage associated with the infarct

- 0 none
- 1 petechial haemorrhage (minor punctate areas of blood density (approx 60 to 80 Hounsfield Units) at the margins of or within the infarct)
- 2 small confluent haematoma < 2 cm in diameter within the infarct
- 3 haematoma > 2 cm in diameter within the infarct

Appendix 4 : Codes for describing the likely pattern of cerebral arterial occlusion suggested by Transcranial Doppler Ultrasound in patients with acute ischaemic stroke.

primary codes describing the symptomatic MCA blood velocity:

- 700 symptomatic MCA velocity 25% > asymptomatic (ie hyperaemia)
- 600 symptomatic MCA blood velocity = asymptomatic
- 500 symptomatic MCA velocity = 50-75% (ie more than 25% reduction) of the asymptomatic MCA blood velocity
- 400 focal high velocity in the symptomatic MCA with decreased velocity superficially (ie focal stenosis)
- 300 symptomatic MCA blood velocity = 25 to 50% of the asymptomatic MCA blood velocity
- 200 symptomatic MCA velocity less than 25% of the asymptomatic MCA blood velocity
- 100 absent symptomatic MCA blood velocity
- 000 absent symptomatic MCA and ACA blood velocity signal

secondary codes (to be used in conjunction with primary) :

- 010 increased velocity ACA on symptomatic side (by 25% more than asymptomatic side)
- 020 increased velocity PCA on symptomatic side (by 25% more than the asymptomatic side)
- 030 increased velocity both ACA and PCA on symptomatic side

tertiary codes describing collateral pathways suggesting ICA disease proximal to the skull base (to be used in conjunction with the primary)

- 001 reversed direction of flow in the ACA on symptomatic side
- 002 reversed ophthalmic artery flow on the symptomatic side
- 003 reversed ACA and ophthalmic artery flow on the symptomatic side

Appendix 5 :

Codes for describing the likely pattern of cerebral arterial occlusion suggested by the isotope Mean Cerebral Transit Time in patients with acute ischaemic stroke.

primary codes describing the abnormalities in the symptomatic hemisphere:

- 700 transit time on the symptomatic side faster than on the asymptomatic
- 600 transit time on the symptomatic side = asymptomatic
- 500 transit time prolonged in the posterior half of the symptomatic side
- 400 transit time prolonged in the middle half of the symptomatic side
- 300 transit time prolonged in the anterior half of the symptomatic side
- 200 transit time prolonged in the entire symptomatic hemisphere

secondary codes (to be used in conjunction with the primary):

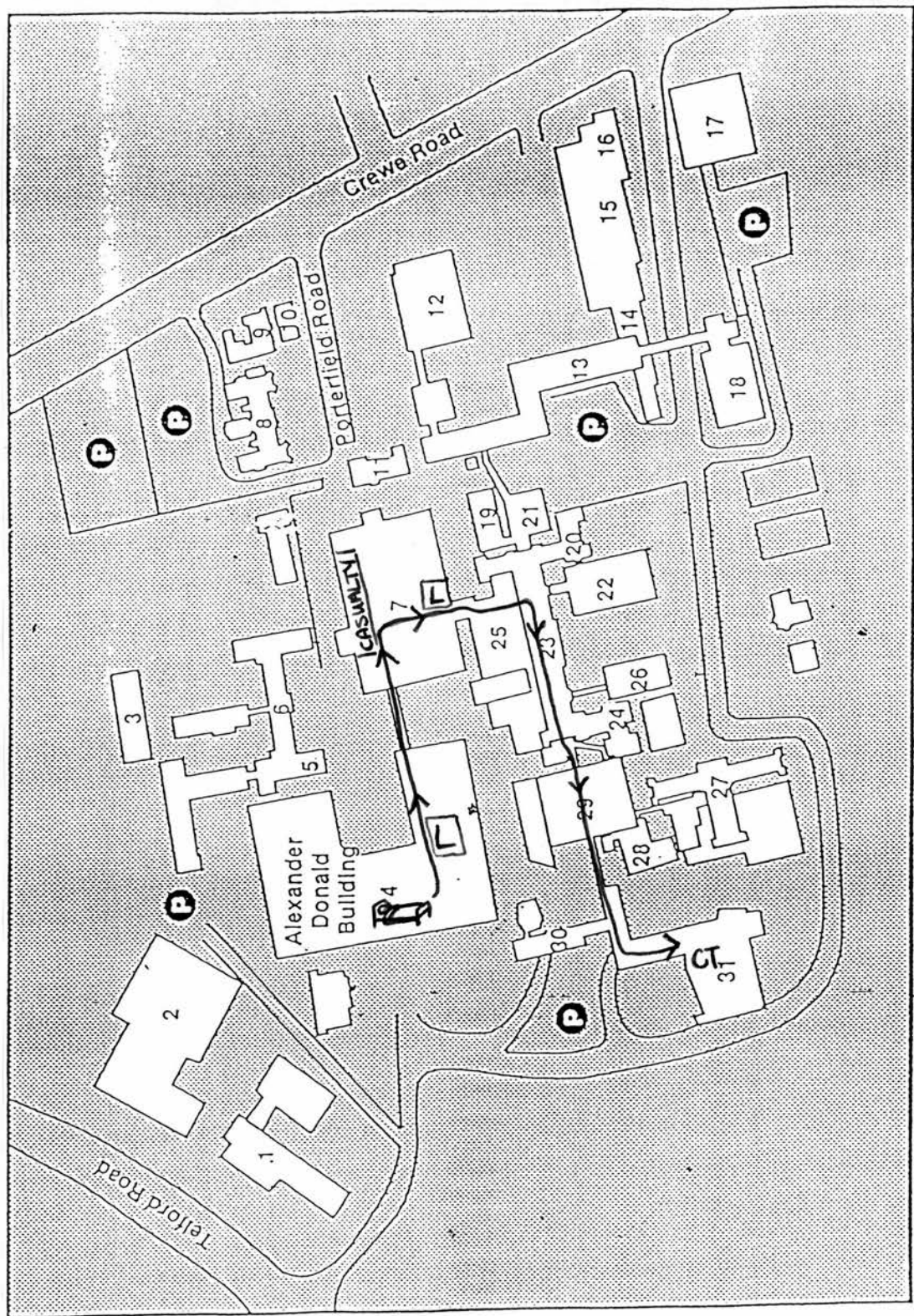
- 020 1 - 2 second difference in transit time between sides
- 010 2 or more seconds difference " " " "
- 030 bilaterally prolonged transit

tertiary code suggesting ICA disease proximal to the skull base :

- 001 loss of the normal antero-posterior gradient

The normal range of hemispheric transit time was 2.5 to 7.7 seconds, with no more than one second difference between equivalent parts of the hemispheres. Transit time was normally faster in the anterior 2/3 to 3/4 of the brain than in the posterior 1/3 to 1/4, therefore loss of the normal anteroposterior gradient indicated that the transit time posteriorly equalled that anteriorly.

Appendix 6 : Map of the Western General Hospital.
The route from the general medical ward to the CT scanner is marked by arrows, with lifts marked "L". The journey takes five minutes walking, but ten minutes pushing a trolley or bed.



Appendix 7 : Consent form for the Thrombolysis Trial.

Streptokinase in Cerebral Infarction Study

Department of Neurology and Neuroradiology

Western General Hospital, Edinburgh.

We would like to explain to you some of the research which we are doing and then ask if you want to help with it.

Background : Every day, all over the country, lots of people come into hospital who have just had a stroke, caused by a blood clot blocking a blood vessel which supplies part of the brain. So far no successful treatment has been found for this. Drugs which could dissolve the blood clot might help. We know that these drugs are very helpful in heart attacks, and we think that they might help patients who have had a stroke. If you agree to take part, then in addition to all the normal treatments which you would have received anyway, you will have special x-rays taken of the blocked blood vessel (angiogram). If the test confirms the blockage clot-dissolving treatment will be given.

What treatment is given? : If the blood vessel is blocked by a clot, you will be given aspirin which will help dissolve the clot (and help prevent new clots forming). In addition some patients will be given an additional treatment with streptokinase which can speed up the clot dissolving process. Other patients will be given treatment with a simple salt solution, this will help us to find out whether aspirin alone is enough to unblock arteries, or whether streptokinase is needed as well.

How the treatment is given? : The special x-rays of the blocked blood vessel (angiogram) are taken by injecting x-ray dye along a small plastic tube placed into the blood vessel system at the top of the leg, and the additional treatment is also given through the same tube. Afterwards, the plastic tubing will be removed. The whole process will take about three quarters of an hour.

Risks : There is a small chance that doing the x-rays of the blood vessels could worsen the stroke, but we are doing only the minimum x-rays required, and believe that the benefits outweigh the risks. The clot dissolving treatment can cause allergic reactions, bleeding, and falls in blood pressure. We are using a very small amount of the drug and believe that these side effects are unlikely.

If you agree that you/your relative should take part in the study, then we would like you to sign this document. This will confirm that we have discussed what is involved, and that you have agreed that you/your relative should take part.

Signature of patient/relative _____

Name (print) _____ Date _____

Signature of doctor explaining procedure _____

Name (print) _____ Date _____

Appendix 8

Glasgow Coma Scale

Eye Opening-	Never	1
	To pain	2
	To sound	3
	Spontaneously	4
Best Motor-	None	1
	Extension to pain	2
	Flexion to pain(abn)	3
	Flexion to pain(n)	4
	Localises to pain	5
	Normal	6
Best verbal	None	1
	Incomprehensible	2
	Inappropriate	3
	Confused	4
	Orientated	5

Conscious level- Reaction Level Scale:

- 1) Alert
No delay in response
Orientated
- 2) Drowsy or confused
Responsive to light stimulation, talk, touch, single shout.
- 3) Very drowsy or confused
Responsive to strong stimulation, repeated shouting, shaking, pain stimulation
- 4) Unconscious:localises but cannot perposefully ward off pain
- 5) Unconscious:withdrawing movements
- 6) Unconscious:stereotyped flexion
- 7) Unconscious:stereotyped extension
- 8) Unconscious:no response to pain

Modified Motricity Index

Arm

Pinch grip-	
No movement	0
Beginnings of prehension	11
Grips (but not against gravity)	19
Against gravity	22
Against pull but weak	26
Normal	33

Elbow flexion (from 90)-

No movement	0
Palpable contraction only	9
Movement not against gravity/limited range	14
Movement against gravity/full range	19
Weaker than other side	25
Normal	33

(use this last scoring for the other movements)

Shoulder abduction (from chest)-

Arm score

Leg

Ankle dorsiflexion (from plantar flexed)-
Knee extension (from 90)-
Hip flexion-

Leg score
Side score

Oxford Handicap Scale (Modified Rankin)

- 0= No symptoms
- 1= Minor symptoms which do not interfere with lifestyle
- 2= Minor handicap-symptoms which lead to some restriction in lifestyle, but do not interfere with the patients' capacity to look after themselves
- 3= Moderate handicap-symptoms which significantly restrict lifestyle and/or prevent totally independent existence
- 4= Moderately severe handicap-symptoms which clearly prevent independent existence though not needing constant attention
- 5= Severe handicap-totally dependent, requiring attention day and night

Barthel Index (with modified scoring)

Code	Criteria
5	Fully independent
4	Minimal help required
3	Moderate help required
2	Attempt task but unsafe
1	Unable

Feeding-

Grooming-

Bowels-

Bladder-

Dressing-

Chair/bed transfer-

Toilet-

Mobility-

if coded "1" score for wheelchair

Wheelchair-

Stairs-

Bathing-

The modified scoring is used and derived from the codes 1 to 5 of each item above.

Appendix 9 : Publications arising from the work in this thesis.

Papers (Where appropriate, the co-authors have given their approval for the inclusion of copies of the published papers in this thesis. No reprints were obtained from the publishers who have indicated their approval also for inclusion of photocopies.)

Wardlaw JM, Warlow CP: Thrombolysis in acute ischaemic stroke : Does it work? *Stroke* 1992;23:1829-1839.

Wardlaw JM, Dennis MS, Lindley RI, Warlow CP, Sandercock PAG, Sellar RJ: Does early reperfusion of a cerebral infarct influence cerebral infarct swelling in the acute stage or the final clinical outcome? *Cerebrovascular Diseases* 1993;3:86-93.

Wardlaw JM, Warlow CP: A meta-analysis of all published data on the use of thrombolytic therapy to treat acute ischaemic stroke. in *Thrombolytic Therapy in Acute Ischaemic Stroke* ed del Zoppo GJ, Mori E, Hacke W, Publ Springer-Verlag New York 1993 pp275-277, ISBN 0-387-56442-X.

Wardlaw JM: Cheyne-Stokes respiration in patients with acute ischaemic stroke : observations on middle cerebral artery blood velocity changes using transcranial Doppler ultrasound. *Cerebrovascular Diseases* in press.

Wardlaw JM, Warlow CP: Thrombolysis in acute ischaemic stroke - Response. *Stroke* 1993;24:911-912.

Wardlaw JM, Dennis MS, Lindley RI, Sellar RJ, Warlow CP: A simple clinical classification of acute ischaemic stroke : accuracy in predicting the site and size of cerebral infarction on CT brain scanning. *J Neurol Neurosurg Psychiat* submitted.

Wardlaw JM, Dennis MS, Murchison JT, Vaughan GT: CT scanning patients with acute stroke : perception versus reality. *Health Trends* submitted

Wardlaw JM, Sellar RJ : A simple practical classification of cerebral infarct morphology as seen on CT brain scans and its interobserver reliability. in preparation for *Am J Neuroradiol*.

Wardlaw JM, Merrick MV, Ferrington C, Dennis MS, Lindley RI, Warlow CP, Sellar RJ: The isotope Mean Cerebral Transit Time : a simple practical method of diagnosing the site and extent of cerebral arterial occlusion in acute ischaemic stroke. in preparation for *Cerebrovascular Diseases*.

Abstracts and Presentations

At the Eurodop'92 meeting in Brighton, UK, 5-8th April 1992:

Wardlaw JM, Warlow CP, Sellar RJ, Allan PL: Potential pitfalls of cervical carotid ultrasound in young patients with acute ischaemic stroke - dissection or embolism? Published in the Proceedings of the Conference, pp 255.

Wardlaw JM: Periodic respiration in patients with acute ischaemic stroke - observations on middle cerebral artery blood velocity changes using transcranial Doppler ultrasound. Published in the Proceedings of the Conference, pp 254.

At the Second International Meeting on Thrombolysis in Acute Ischaemic Stroke, La Jolla, California, USA, 1-2 May, 1992:

A meta-analysis of all published data on the use of thrombolytic therapy to treat acute ischaemic stroke. Published in the Conference Proceedings (see above).

At the Second European Stroke Conference, Lausanne, Switzerland, 25-27 June 1992:

Wardlaw JM, Lindley RI, Warlow CP, Dennis MS, Sellar RJ: Swelling in acute ischaemic stroke and reperfusion : a prospective study in patients with large infarcts. *Cerebrovascular Diseases* 1992;2:197

Wardlaw JM, Dennis MS, Lindley RI, Merrick MV, Sellar RJ, Warlow CP: The isotope cerebral transit time : further evaluation in acute ischaemic stroke. *Cerebrovascular Diseases* 1992;2:224.

Wardlaw JM, Warlow CP: An overview of all the published randomised trials of thrombolytic drugs in acute ischaemic stroke. *Cerebrovascular Diseases* 1992;2:198.

At the 16th World Congress of the International Union of Angiology, Paris, 12-18th September 1992: Oral presentation entitled: "Thrombolysis in Acute Ischaemic Stroke".

At the Second International Conference on Stroke, Geneva 12-15 May, 1993:

Wardlaw JM, Sellar RJ: Introducing a simple practical classification of cerebral infarcts as seen on CT brain scans.

Published in the Proceedings of the Conference, pp 23.

Wardlaw JM, Dennis MS, Lindley RI, Sellar RJ, Warlow CP: How accurate is a simple clinical classification for predicting the site and extent of cerebral infarction in routine hospital practice? Published in the Proceedings of the Conference, pp 64.

At the Annual Meeting of the Association of British Neurologists, London, 29th September - 2nd October 1993:

Wardlaw JM, Lindley RI, Warlow CP, Sandercock PAG, Dennis MS: A pilot study of intra-arterial thrombolysis for acute ischaemic stroke. to be published in J Neurol Neurosurg, Psychiat with the Conference Proceedings in due course.

Comments, Opinions, and Reviews

Thrombolysis in Acute Ischemic Stroke: Does It Work?

J.M. Wardlaw, MRCP, FRCR, and C.P. Warlow, FRCP

Background: This article is presented to provoke further discussion regarding the use of thrombolytic drugs to treat acute ischemic stroke.

Summary of Review: Overview analysis of the six randomized trials of thrombolysis in acute ischemic stroke available in the world literature shows a 20% increase in the odds of death and a 30% reduction in the odds of death or deterioration (both with wide confidence intervals, neither result significant) after thrombolytic treatment for acute ischemic stroke. Exclusion of the two trials conducted without the benefit of computed tomographic scanning shows a 37% reduction in the odds of death (95% confidence interval, 74% reduction to 40% excess) and a significant reduction of 56% in the odds of death or deterioration after thrombolytic treatment (95% confidence interval, 20–76% reduction; $2p=0.007$). Analysis of all published studies (randomized and nonrandomized) shows that there does not appear to be an excess risk of hemorrhagic transformation of the cerebral infarct or of severe edema formation.

Conclusions: We believe the present evidence is sufficiently encouraging to warrant proper testing of thrombolysis in sufficiently large and well-designed randomized clinical trials to influence clinical practice. (*Stroke* 1992;23:1826–1839)

KEY WORDS • cerebral ischemia • clinical trials • thrombolytic therapy

Stroke has defied the considerable efforts of medical science to find an effective treatment and remains the third most common cause of death in the developed world, preceded only by ischemic heart disease and all cancers combined.¹ However, unlike ischemic heart disease and cancer, stroke leaves many more people disabled and dependent on family and social or health services. Despite a decline in stroke mortality in some but not all countries,¹ there is rather little evidence of a decline in incidence.² Therefore, anticipated demographic changes, and thus increasing stroke numbers, make it even more important to find an effective treatment.³

Therapeutic approaches should reflect logical application of our present understanding of the sequence of events in the ischemic brain leading to cerebral infarction. After interruption of the blood supply, some tissue probably suffers irreparable damage within minutes, but a variable amount remains in a "shut-down" but viable state for several hours.⁴ The concept of this "ischemic penumbra" is now reasonably well established by electrophysiological work in animals⁴ and positron emission tomography.⁵ Neutralization of toxic metabolites released from infarcted cells or restoration of the blood supply might save the ischemic tissue and improve

outcome. Thus two basic approaches have evolved: 1) to protect ischemic but still viable neurons from further damage by toxic metabolites and 2) to improve the blood supply to ischemic brain.

Using the first approach, nimodipine has not been shown to be of any benefit in moderately large groups of patients.⁶ Newer excitatory amino acid antagonists are being evaluated but may have unacceptable toxicity (e.g., psychosis and cardiac arrhythmias), and it remains to be seen whether the benefit in animals can be translated into benefit in elderly stroke patients.⁷

Using the second approach, hemodilution is ineffective in the generality of ischemic stroke patients.⁸ Antithrombotic therapy (with heparin, warfarin, or aspirin) has not been properly tested in large randomized clinical trials. Although variably used in acute stroke,⁹ we do not know if these drugs improve outcome. A randomized trial of aspirin and heparin in acute ischemic stroke has begun in Europe.

That leaves thrombolysis, a theoretically attractive treatment with proven ability to dissolve arterial thrombus elsewhere in the body¹⁰ but with the potentially unattractive adverse effect of converting a simple (pale) infarct into a hematoma. Thrombolytic drugs were first used in the late 1950s for acute stroke.¹¹ Since then over 2,800 patients have been reported in the world literature. Despite this we do not know if thrombolysis works, nor what the risks of treatment are. Most of the literature consists of case reports or small series, with only six small randomized trials.^{12–17} Rather than review historically the use of thrombolytic drugs to treat cerebral ischemia,¹⁸ it is our intention to examine critically and quantitatively the evidence that thrombolytic drugs might work in acute ischemic stroke without unacceptable risks.

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Given the heterogeneity of the pathogenesis and outcome of acute ischemic stroke and that the magnitude of any treatment effect may be modest, both a proper control group and adequate numbers of patients are essential to ensure an unbiased and precise trial result.¹⁹ Many of the reported studies have methodological inadequacies that make their evaluation of thrombolysis in acute stroke inconclusive. We hope to demonstrate in this article that thrombolysis has a good chance of improving outcome in acute ischemic stroke without unacceptable risk, and that properly conducted large randomized trials (on the scale of the myocardial infarction thrombolysis trials) would be reasonable to do and likely to yield a definitive answer; indeed, several less ambitious trials have already started (see below).

Why Might Thrombolysis Work?

The majority of acute focal cerebral ischemic events are due to embolism or in situ thrombosis.²⁰ A small proportion are due to "boundary zone" ischemia secondary to a hypotensive episode or internal carotid artery (ICA) occlusion. Approximately 20% are small subcortical infarcts commonly attributed to degenerative changes in small perforating arteries,²¹ although some authors dispute this. Most of the discussion in this article will refer to large artery territory thromboembolic stroke.

Thrombolytic drugs work in acute myocardial infarction, which is usually due to acute thrombotic occlusion of a coronary artery, by lysing the thrombus quickly and restoring vessel patency.²² The Second International Study of Infarct Survival (ISIS-2) showed that streptokinase (SK) reduced mortality after myocardial infarction by 25%.²³ Aspirin confers similar benefit, and the effect of both is a 50% reduction in mortality at 5 weeks. The cause of many acute ischemic strokes, as outlined above, is acute embolic or thrombotic cerebral artery occlusion. Therefore, there are good theoretical reasons why thrombolysis might also work in the cerebral circulation.

In the brain, the information on spontaneous recanalization of thrombotic or embolic cerebral artery occlusion is scanty. Based on the limited evidence available from Caucasian populations, about 20% of presumed embolic (cardiac or artery-to-artery) middle cerebral artery (MCA) occlusions (main stem or branch) may recanalize spontaneously within 24 hours, and possibly as many as 80% do so within 1 week of onset,^{24,25} but these figures are no more than "best estimates." It is difficult to extract the spontaneous lysis rate of artery-to-artery embolism from the figures for cardiac embolism (often patients have both potential sources), and there is little information on recanalization of acute ICA occlusions in the neck. Spontaneous reperfusion after thrombotic cerebral artery occlusion (thought to be more common in Oriental peoples) has been little studied but appears to be less likely than recanalization after embolic occlusion.^{26,27} Therefore, in the population with ischemic stroke due to large vessel disease, the spontaneous recanalization rate will be at best approximately 20% at 24 hours but may depend on the location of the occlusion (ICA or MCA), its composition (fibrin embolus, platelet embolus, or thrombus), and its age. Although these figures emphasize the lack of information regarding spontaneous recanalization of occluded cerebral arteries, there is clear evi-

dence that spontaneous lysis of thrombus does occur. So the question for thrombolytic therapy is whether this spontaneous process can be accelerated in time to restore useful brain function without unacceptable risk.

What Do We Know So Far From Using Thrombolytic Drugs in Ischemic Stroke?

There have been over 60 reports in the world literature to date. Six were randomized trials,¹²⁻¹⁷ and four had retrospective or nonrandom control groups.²⁸⁻³¹ Of the remaining, 35 or more were so-called open trials and approximately 20 were case reports. The trials were identified by literature search (using *Index Medicus*), by tracing references cited in thrombolysis articles, and by discussion with other researchers interested in thrombolysis. All published randomized trials are included in this analysis as well as all nonrandomized trials and most case reports in the English, French, German, and Japanese literature. It is probable that some acute stroke patients have been treated with thrombolysis but not reported in the literature, and potential bias because of this must be borne in mind when interpreting the following analysis.³²

Randomized Trials

Of the six randomized trials shown in Table 1 and Figure 1, the two by Meyer et al^{12,13} were conducted before the invention of computed tomographic (CT) scanning, and therefore some patients with primary intracerebral hemorrhage or hemorrhagic infarction may inadvertently have been included. The numbers were small, and the outcome measure was clinical evaluation at 10 days, which may be too early for valid assessment. In the first study there was no difference in outcome between the treated and control groups. In the second, larger study, the treated group fared worse. However, patients were included up to 72 hours after onset, and although the mean time to treatment was not stated, trial intervention may have been too late. It is generally thought that treatment for acute ischemic stroke should begin as soon as possible, certainly within 24 hours of onset.

The randomized trials by Mori et al,¹⁴ Ohtomo et al,¹⁵ Abe et al,¹⁶ and the Japanese Thrombolysis Study Group (JTSG)¹⁷ used CT scanning to exclude intracerebral hemorrhage as a cause of stroke before randomization and for follow-up after treatment. Mori et al studied MCA and ICA recanalization and found that nine of 19 patients given intravenous tissue plasminogen activator (t-PA) within 6 hours of symptom onset recanalized compared with three of 12 given placebo. Ohtomo et al published a Japanese multicenter randomized trial of low-dose intravenous urokinase (UK) in acute thrombotic cerebral infarction given within 5 days of symptom onset. Abe et al (also Japanese) published a randomized trial of intravenous urokinase for acute ischemic stroke given up to 30 days after symptom onset (more than half of the patients were treated 4 days or more after onset). The JTSG¹⁷ studied clinical improvement after embolic stroke and found that 37 of 51 patients randomized to 34 mg t-PA i.v. improved compared with 26 of 47 given placebo within 6 hours of symptom onset. Additional information on drug, dosage, route of administration, time to treatment, and outcome measure is given in Table 1. Note

TABLE 1. "Controlled" Trials of Thrombolysis for Acute "Ischemic" Stroke

Author	Drug	Route	Dose	Time from onset	Outcome measure	Results			
						Treated		Control	
						No.	%	No.	%
<i>Randomized</i>									
Meyer ¹²	Fib/ Pla	IV	2.5–11.5 ×10 ⁵ units	<72 hours	Clinical improvement at 10 days	20	45	20	45
Meyer ¹³	SK	IV	2.5–17.5 ×10 ⁵ units	<72 hours	Clinical improvement at 10 days	37	43	36	58
Mori ¹⁴	t-PA	IV	34–50 mg	<6 hours	Recanalization	19	47	12	25
Ohtomo ¹⁵	UK	IV	6×10 ⁴ units per day for 7 days	<5 days	Clinical improvement at 4 weeks	169	56	181	42
Abe ¹⁶	UK	IV	6×10 ⁴ units per day for 7 days	<30 days	Clinical improvement at 1 and 4 weeks	54	63	53	43
JTSG ¹⁷	t-PA	IV	34 mg	<6 hours	Clinical improvement at 4 weeks	51	72	47	55
<i>Nonrandomized</i>									
Hacke ²⁸	SK/ UK	IA	4×10 ⁵ units approx.	<24 hours	Clinical improvement	45	44	23	0
Okada ²⁹	t-PA	IV	26–50 mg	<6 hours	Clinical improvement at 1 month	15	47	11	9
Abe ³⁰	UK	IV	6–12 ×10 ⁵ units	Up to 6 months	Clinical improvement at 1 month	62	71	22	36
Larcan ³¹	UK	IV	16.5–38.5 ×10 ⁵ units	36 hours+	Clinical improvement	36	47	41	17

No., total number of patients in each group; %, % of patients who improved clinically, or recanalized.¹⁴ Where two assessment times are given, the % improved refers to the later time. JTSG, Japanese Thrombolysis Study Group; Fib, fibrinolysin; Pla, plasmin; SK, streptokinase; t-PA, tissue-type plasminogen activator; UK, urokinase; IV, intravenous; IA, intra-arterial.

that Table 1 includes not only the six truly randomized trials (upper half) but also the four nonrandomized trials (described below), which are often referred to as "controlled" trials in the literature to emphasize the distinction.

Figure 1 shows the results of an overview analysis³³ of death (Figure 1A) and death or deterioration (Figure 1B) after thrombolytic therapy for acute ischemic stroke. The analysis is of published results for the six randomized trials, and additional information was supplied by E. Mori and T. Yamaguchi for the JTSG. Although deterioration was assessed differently in each trial, the overview technique minimizes the problem of trying to compare different trials and end point measures by not comparing randomized, controlled trials directly with each other. Rather, the overview compares the magnitude and direction of any treatment effect contained within the individual trials and yields an estimate of the overall treatment effect.

Analysis of all six trials shows that the risk of death is increased by 20% with thrombolysis but with a wide confidence interval (CI) that includes the possibility of 31% reduction to 151% excess. The risk of death or deterioration (all six trials) is reduced by 37% with thrombolysis, but the wide CI includes the possibility of 66% reduction to 14% excess.

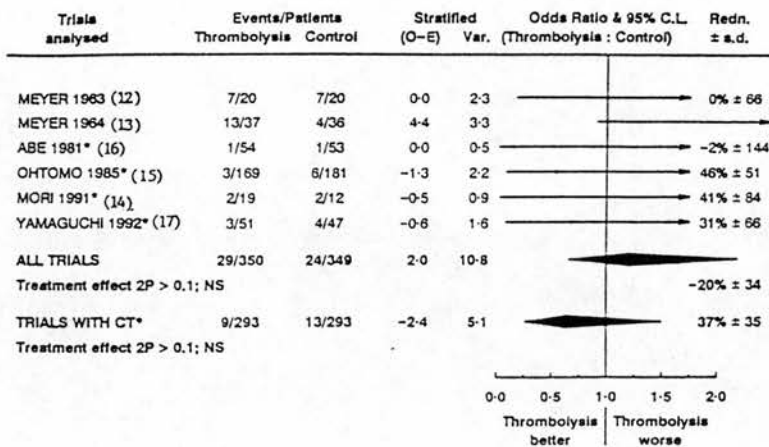
Analysis of the four trials conducted with the benefit of CT scanning (therefore reliably excluding cerebral

hemorrhage as the cause of symptoms) shows a reduction in the risk of death of 37% (95% CI, 74% reduction to 47% excess) with thrombolytic treatment and shows a reduction in the risk of death or deterioration of 56% (95% CI, 20–76% reduction [$2p=0.007$]). This provides some evidence that thrombolysis is beneficial in acute ischemic stroke; this benefit is not enough to recommend routine treatment but certainly enough to encourage larger randomized trials.

Studies With a Retrospective or Nonrandom Control Group

The study by Hacke et al²⁸ on vertebrobasilar occlusion illustrates the difficulty of including a retrospective control group (Table 1). Although the treated and control groups were similar in many respects, 12 of 22 (54%) of the control subjects were unconscious at diagnosis and entry into the trial compared with 15 of 43 (35%) of the treated group, perhaps reflecting increasing awareness of the condition and earlier diagnosis. Epidemiological studies have shown that vertebrobasilar stroke can cause mild symptoms and does not always progress to coma with the uniformly bleak outcome that Hacke et al have suggested.³⁴ Therefore, the prospective treated and retrospective control patients may have been different in prognosis, and it is not valid to use the sicker group treated conventionally as a control for the later treated group. The other three studies that in-

A: THROMBOLYSIS FOR ACUTE "ISCHAEMIC" STROKE
THROMBOLYSIS vs CONTROL: MORTALITY



B: THROMBOLYSIS FOR ACUTE "ISCHAEMIC" STROKE
THROMBOLYSIS vs CONTROL: DEATH OR DETERIORATION

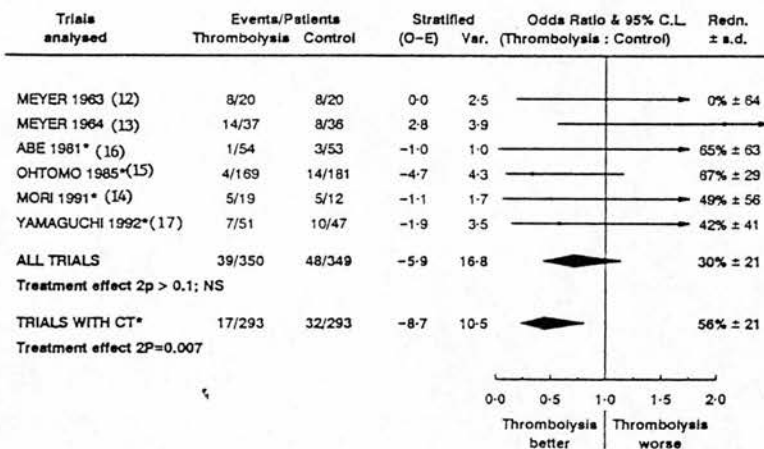


FIGURE 1. Overview analysis of the randomized trials of thrombolysis for acute ischemic stroke. Panel A: Odds of death; panel B: odds of death or deterioration for thrombolytic therapy vs. placebo. Note that the two trials by Meyer were done without computed tomographic (CT) scanning. "Yamaguchi" refers to the Japanese Thrombolysis Study Group trial. O-E, observed minus expected number of events in the treated group; Var, variance; Redn, reduction. An odds ratio <1 indicates that thrombolytic treatment may be beneficial, and the confidence limit (C.L.) gives the 95% confidence interval for the odds ratio indicating the range of possible therapy effects.

cluded a control group (Table 1) did not state how the patients were chosen or how treatment was allocated.²⁹⁻³¹

Open Trials and Case Reports

The primary aim of the studies shown in Tables 2 and 3 was to assess safety and find an optimal dose. They are a heterogeneous group of reports, some using the intravenous and some the intra-arterial route of drug administration, with different drugs, doses of drug, inclusion criteria, and outcome events (recanalization or clinical improvement). It is not possible to make any comment about benefit because there were no control groups. It is even difficult to draw any conclusions about safety because the natural history of cerebral infarction is so variable and there were no control subjects with which the development of cerebral edema or hemorrhagic transformation could be compared.

The studies that examined reperfusion (using serial angiography) considered together showed some degree of recanalization (partial or complete) in 61% of patients within 24 hours of symptom onset. This appears to

be better than the estimated spontaneous rate of recanalization of 20% at 24 hours after onset (see above). It is encouraging that 61% recanalization is of the same order of magnitude as was found in the acute myocardial infarction thrombolysis studies, which used angiography to assess recanalization.⁷⁰ Although these figures are very tentative, all available data are included and suggest the presence of a useful treatment effect.

These conclusions are encouraging but tentative, the numbers of patients are small, and there may have been publication bias,³² although in the field of thrombolysis in acute ischemic stroke positive as well as negative results seem to be presented with equal enthusiasm.

Does Thrombolysis Increase the Risk of Cerebral Hemorrhage?

Thrombolytic drugs given for extracranial vascular disease increase the risk of hemorrhage both in the brain and elsewhere in the body.²³ Therefore, thrombolysis for acute ischemic stroke might increase the risk of cerebral hemorrhage, but how big is this risk? Thrombolysis might, by reducing infarct size or other mecha-

TABLE 2. Open Studies of Thrombolysis for Acute Ischemic Stroke: Recanalization

Author	Year	Drug	Route	Dose	No. of patients	Percent recanalized
Del Zoppo ³⁵	1988	SK	IA	0.06–2.5×10 ⁵ units	20	75
Theron ³⁶	1989	SK	IA	0.25–1.5×10 ⁵ units	12	100
Maisa ³⁷	1988	SK	IA	2.5×10 ⁵ units	16	100
Zeumer ³⁸	1985	SK/UK	IA	Various	29	86
Berg-Dammer ³⁹	1991	SK	IA	10 ⁵ units	3	100
Baird ⁴⁰	1992	SK	IV	1.5×10 ⁵ units	5	38
Total for SK 75/93=80% recanalized						
Zeumer ⁴¹	1984	UK	IA	5–7.5×10 ⁵ units	2	10
Mori ⁴²	1990	UK	IA	1.8–3.2×10 ⁵ units	48	44
Lehmann ⁴³	1989	UK	IA	2–3×10 ⁵ units	10	80
Ikeda ⁴⁴	1990	UK	IA	4.2×10 ⁵ units	13	85
Siepmann ⁴⁵	1991	UK	IA	Up to 7.5×10 ⁵ units	11	64
Casto ⁴⁶	1992	UK	IA	5.6×10 ⁵ units	4	80
Berg-Dammer ³⁹	1991	UK	IA	2–7.5×10 ⁵ units	7	100
Mobius ⁴⁷	1991	UK	IA	3–9.5×10 ⁵ units	18	77
Seikmann ⁴⁸	1991	UK	IA	8×10 ⁵ units	2	100
Matsumoto ⁴⁹	1991	UK	IA	2.4–12×10 ⁵ units	52	58
Miyakawa ⁵⁰	1984	UK	IV/IA	7–9×10 ⁵ units	49	59
Williams ⁵¹	1992	UK	IA	5–10×10 ⁵ units	2	66
Total for UK 139/222=62% recanalized						
ASSG ⁵²	1992	t-PA	IV	12.5–44 mg	93	36
Karnik ⁵³	1992	t-PA	IA	20 mg	1	100
Yamaguchi ⁵⁴	1991	t-PA	IV	10, 20, 30 mg	58	43
Hennerici ⁵⁵	1991	t-PA	IV	70 mg	18	44
von Kummer ⁵⁶	1991	t-PA	IV	70 or 100 mg	27	56
Brucker ⁵⁷	1992	t-PA	IV	100 mg	25	89
von Kummer ⁵⁸	1992	t-PA	IV	100 mg	32	53
Total for t-PA 154/284=54% recanalized						
Total all patients 368/599=61% recanalized						

Studies are listed according to drug used and increasing dose. No. of patients, total number of patients in study; ASSG, Acute Stroke Study Group; SK, streptokinase; UK, urokinase; t-PA, tissue-type plasminogen activator; IA, intra-arterial; IV, intravenous.

nism, actually reduce the rate of hemorrhagic transformation of the cerebral infarct.⁷¹ There is relatively little good information on the "natural" rate of hemorrhagic transformation of acute ischemic strokes. Most reported studies are limited by the method of patient selection, for example, postmortem series, retrospective CT studies, and some prospective CT studies in which only patients who deteriorated were scanned. In addition, most studies include some patients who received antithrombotic treatment of some sort, and thus for several reasons these studies may have overestimated the frequency of hemorrhagic transformation. There is only one prospective study that used serial CT scanning at predetermined intervals after acute ischemic stroke (regardless of symptoms), and it suggested that approximately 5% of simple (pale) infarcts undergo symptomatic hemorrhagic transformation with formation of space-occupying hematomas⁷² (some patients in that study also received antithrombotic treatment). Pathological studies show some degree of petechial hemor-

rhage in almost all infarcts, although CT scanning detects this less frequently.^{71,73} Petechial hemorrhage is thought to be asymptomatic and thus probably is not clinically important, although this has not been studied. Based on the best information available, we estimate that the spontaneous rate of symptomatic hemorrhagic transformation of the infarct is approximately 5%⁷² and that the rate of asymptomatic (petechial) hemorrhagic transformation is between 15% and 45%,⁷³ but this may be an overestimate. The rate probably varies with the extent of the infarct⁷¹ and possibly with stroke etiology.⁷³

Using all the published data available, we have estimated the rate of hemorrhagic transformation after thrombolysis for acute ischemic stroke (Tables 4 and 5). The true rate of hemorrhagic transformation can only be found from large randomized, controlled trials (including at least several thousand patients), but summing all the data available at present may at least give an estimate of the likely order of magnitude of hemor-

TABLE 3. Open Studies of Thrombolysis for Acute "Ischemic" Stroke: Clinical Outcome

Author	Year	Drug	Route	Dose	No. of patients	Percent improved clinically
Del Zoppo ³⁵	1988	SK	IA	0.6–2.5×10 ⁵ units	20	75
Theron ³⁶	1989	SK	IA	0.25–1.5×10 ⁵ units	12	83
Berg-Dammer ³⁹	1991	SK	IA	10 ⁵ units	3	100
Maisa ³⁷	1988	SK	IA	1–2.5×10 ⁵ units	15	73
Total for SK 39/50=78% improved						
Terashi ⁵⁹	1990	UK	IV	6×10 ⁴ units/day for 7 days	171	35
Yamaguchi ⁵⁴	1991	UK	IV	6×10 ⁴ units/day for 7 days	77	45
Abe ⁶⁰	1981	UK	IV	6×10 ⁴ units/day for 7 days	51	70
Fukase ⁶¹	1972	UK	IV	10 ⁴ –10 ⁵ units	949	68
Mori ⁴²	1990	UK	IA	1.8–3.2×10 ⁵ units	22	55
Lehmann ⁴³	1989	UK	IA	2–3×10 ⁵ units	10	70
Fujishima ⁶²	1986	UK	IV	3×10 ⁵ units	143	79
Ikedo ⁴⁴	1990	UK	IA	4.2×10 ⁵ units	13	53
Mobius ⁴⁷	1989	UK	IA	2×10 ⁵ units	14	71
Mihara ⁶³	1982	UK	IV	3×10 ⁵ units	33	78
Abe ⁶⁰	1981	UK	IV	6×10 ⁵ units/day for 7 days	49	80
Berg-Dammer ³⁹	1991	UK	IA	2–7.5×10 ⁵ units	7	57
Siepmann ⁴⁵	1991	UK	IA	7.5×10 ⁵ units	11	64
Zeumer ³⁸	1985	UK/SK	IA	Various	29	59
Zeumer ⁴¹	1989	UK	IA	2.5–7.5×10 ⁵ units	7	57
Matsumoto ⁴⁹	1991	UK	IA	2.4–12×10 ⁵ units	52	59
Miyakawa ⁵⁰	1984	UK	IV/IA	7–9×10 ⁵ units	49	45
Williams ⁵¹	1992	UK	IA	5–10×10 ⁵ units	3	33
Fletcher ⁶⁴	1976	UK	IV	1.4–3.3×10 ⁶ units	31	52
Nenci ⁶⁵	1983	UK	IV	1.7×10 ⁶ units	4	75
Labauge ⁶⁶	1978	UK	IV	6–34.5×10 ⁵ units	24	42
Total for UK 1133/1747=65% improved						
Terashi ⁵⁹	1990	t-PA	IV	6 mg/day for 7 days	171	59
Ohtomo ⁶⁷	1988	t-PA	IV	6–10 mg/day for 7 days	131	69
Yamaguchi ⁵⁴	1991	t-PA	IV	1.7–3.4 mg/day for 7 days	145	66
NIH Study ^{68a,68b}	1992	t-PA	IV	50–70 mg	94	26
Hennerici ⁵⁵	1991	t-PA	IV	70 mg	18	28
von Kummer ⁵⁶	1991	t-PA	IV	70 or 100 mg	27	35
Overgaard ⁶⁹	1992	t-PA	IV	100 mg	21	85
Brucker ⁵⁷	1992	t-PA	IV/IA	100 mg	28	29
von Kummer ⁵⁸	1992	t-PA	IV	100 mg	32	44
Total for t-PA 373/667=56% improved						
Total all patients 1,545/2,464=63% improved						

Studies are listed according to drug used and increasing dose. Various different measures were used to determine clinical improvement, and patients with various types of acute ischemic stroke syndrome were included. NIH, National Institutes of Health; No. of patients, total number of patients in study; SK, streptokinase; UK, urokinase; t-PA, tissue-type plasminogen activator; IA, intra-arterial; IV, intravenous.

rhagic transformation. All the data, including case reports, have been included to give as unbiased an assessment as can be obtained at present. Note that the time to treatment, duration of treatment, route of administration, type of drug, and total dose of thrombolytic drug (in some studies very low doses of thrombolytic drug were used), definition of symptomatic and asymptomatic hemorrhagic transformation, and patient characteristics were different in each study. Therefore, this

analysis can only provide an estimate of the likely hemorrhagic transformation rate. Table 4 shows the rate of asymptomatic petechial hemorrhagic transformation (without clinical deterioration), and Table 5 shows the rate of symptomatic intracerebral hematoma formation (with clinical deterioration) after thrombolysis. Note the huge variation in the reported rate of asymptomatic petechial hemorrhage. This may partly reflect bias in interpretation of CT scans, or it may be

TABLE 4. Asymptomatic Intracerebral Petechial Hemorrhage After Thrombolysis for Acute Ischemic Stroke

Author	Year	Drug	Route	Dose	No. of patients	Percent affected
Del Zoppo ³⁵	1988	SK	IA	0.06–2.5×10 ⁵ units	20	20
Zeumer ³⁸	1985	SK/UK	IA	Various	29	17
Theron ³⁶	1989	SK	IA	0.25–1.5×10 ⁵ units	12	16
Berg-Dammer ³⁹	1991	SK	IA	10 ⁵ units	3	0
Maisa ³⁷	1988	SK	IA	2×10 ⁵ units	16	0
Hacke ²⁸	1988	SK	IA	4×10 ⁵ units	45	5
Frink ⁷⁴	1990	SK	IV	1.5×10 ⁶ units	1	0
Total for SK 11/124=9% petechial hemorrhage						
Yamaguchi ⁵⁴	1991	UK	IV	6×10 ⁴ units/day for 7 days	77	5
Ohtomo ¹⁵	1985	UK	IV	6×10 ⁴ units/day for 7 days	169	1
Harenberg ⁷⁵	1979	UK	IA	1.5×10 ⁵ units	1	0
Mori ⁴²	1990	UK	IA	1.8–3.3×10 ⁵ units	43	12
Jungreis ⁷⁶	1989	UK	IA	2.1×10 ⁵ units	1	0
Lehmann ⁴³	1989	UK	IA	2–3×10 ⁵ units	10	0
Fujishima ⁶²	1986	UK	IV	3×10 ⁵ units	143	0
Ikeda ⁴⁴	1990	UK	IA	4.2×10 ⁵ units	13	0
Casto ⁴⁶	1992	UK	IA	5.6×10 ⁵ units	5	20
Berg-Dammer ³⁹	1991	UK	IA	6–7×10 ⁵ units	10	20
Siepmann ⁴⁵	1991	UK	IA	7.5×10 ⁵ units	11	30
Zeumer ⁴¹	1989	UK	IA	5–7.5×10 ⁵ units	7	14
Abe ³⁰	1984	UK	IV	6–12×10 ⁵ units	62	0
Seikmann ⁴⁸	1991	UK	IA	8×10 ⁵ units	2	0
Miyakawa ⁵⁰	1984	UK	IA/IV	7–9×10 ⁵ units	49	26
Matsumoto ⁴⁹	1991	UK	IA	2.4–12×10 ⁵ units	52	20
Nenci ⁶⁵	1983	UK	IV	1.7×10 ⁶ units	4	0
Total for UK 46/867=5% petechial hemorrhage						
Yamaguchi ⁵⁴	1991	t-PA	IV	1.7–3.4 mg/day for 7 days	145	0
Yamaguchi ⁵⁴	1991	t-PA	IV	17–51 mg	58	21
ASSG ⁵²	1992	t-PA	IV	12.5–44 mg	104	20
Bruckmann ⁷⁷	1989	t-PA	IV	25.9 mg	1	100
Okada ²⁹	1991	t-PA	IV	26–56 mg	15	33
JTSG ¹⁷	1992	t-PA	IV	34 mg	51	39
Mori ¹⁴	1991	t-PA	IA	34 or 50 mg	19	66
Buteux ⁷⁸	1988	t-PA	IA	50 mg	1	100
NIH Study ^{68a,68b}	1992	t-PA	IV	50–70 mg	94	10
von Kummer ⁵⁶	1991	t-PA	IV	70 or 100 mg	27	22
von Kummer ⁵⁸	1992	t-PA	IV	100 mg	32	28
Turrin ⁷⁹	1991	t-PA	IV	100 mg	1	0
Overgaard ⁶⁹	1992	t-PA	IV	100 mg	21	0
Wildemann ⁸⁰	1990	t-PA	IV	100 mg	1	0
Herderschee ⁸¹	1991	t-PA	IV	100 mg	2	50
Henze ⁸²	1987	t-PA	IA	100 mg	1	0
Brucker ⁵⁷	1992	t-PA	IV	100 mg	28	25
Jafar ⁸³	1991	t-PA	IV	150 mg	1	0
Total for t-PA 101/582=17% petechial hemorrhage						

Grand total all drugs 158/1,573=10% petechial hemorrhage

Only studies that included routine computed tomographic (CT) brain scans after treatment are included (thus excluding all studies before the invention of CT scanning). Studies are listed according to drug used and increasing dose. No. of patients, total numbers of patients in study; ASSG, Acute Stroke Study Group; JTSG, Japanese Thrombolysis Study Group; NIH, National Institutes of Health; SK, streptokinase; UK, urokinase; t-PA, tissue-type plasminogen activator; IA, intra-arterial; IV, intravenous.

TABLE 5. Intracerebral Hematoma With Clinical Deterioration Complicating Thrombolysis for Acute "Ischemic" Stroke

Author	Year	Drug	Route	Dose	No. of patients	Percent affected
Sussman ¹¹	1958	F	IV/IA	Various	3	0
Clarke ⁸⁴	1960	F	IV/IA	2–10×10 ⁵ units	10	0
Meyer ¹²	1963	T	IV	2×10 ⁵ units	20	5
Atkin ⁸⁵	1964	F	IA	5×10 ⁵ units	1	0
Del Zoppo ³⁵	1988	SK	IA	0.6–2.5×10 ⁵ units	20	0
Theron ³⁶	1989	SK	IA	0.25–1.5×10 ⁵ units	12	8
Berg-Dammer ³⁹	1991	SK	IA	10 ⁵ units	3	0
Maisa ³⁷	1988	SK	IA	2×10 ⁵ units	16	6
Hacke ²⁸	1988	SK	IA	4×10 ⁵ units	45	4
Meyer ¹³	1964	SK	IV	2.5–7.5×10 ⁵ units	37	3
Frink ⁷⁴	1990	SK	IV	1.5×10 ⁶ units	1	0
Total for SK 7/135=5% cerebral hematoma						
Yamaguchi ⁵⁴	1991	UK	IV	6×10 ⁴ units/day for 7 days	77	1
Ohtomo ¹⁵	1985	UK	IV	6×10 ⁴ units/day for 7 days	169	0
Abe ⁶⁰	1981	UK	IV	6–60×10 ⁴ units/day for 7 days	101	1
Hass ⁸⁶	1966	UK	IA	10 ⁵ units	1	100
Harenberg ⁷⁵	1979	UK	IV	1.5×10 ⁵ units	1	0
Mori ⁴²	1990	UK	IA	1.8–3.2×10 ⁵ units	43	9
Jungreis ⁷⁶	1989	UK	IA	2.1×10 ⁵ units	1	0
Lehmann ⁴³	1989	UK	IA	2–3×10 ⁵ units	10	0
Mihara ⁶³	1982	UK	IV	3×10 ⁵ units	33	0
Fujishima ⁶²	1986	UK	IV	3×10 ⁵ units	143	0.6
Ikeda ⁴⁴	1990	UK	IA	4.2×10 ⁵ units	13	23
Casto ⁴⁶	1992	UK	IA	5.6×10 ⁵ units	5	0
Berg-Dammer ³⁹	1991	UK	IA	2–7.5×10 ⁵ units	7	0
Abe ³⁰	1984	UK	IV	6–12×10 ⁵ units	86	1
Abe ¹⁶	1981	UK	IV	6×10 ⁴ units/day for 7 days	106	0.9
Siepmann ⁴⁵	1991	UK	IA	7.5×10 ⁵ units	11	0
Zeumer ⁴¹	1989	UK	IA	7.5×10 ⁵ units	7	0
Seikmann ⁴⁸	1991	UK	IA	8×10 ⁵ units	2	0
Matsumoto ⁴⁹	1991	UK	IA	2.4–12×10 ⁵ units	52	12
Fletcher ⁶⁴	1976	UK	IV	1.4–3.3×10 ⁶ units	31	12
Nenci ⁶⁵	1983	UK	IV	1.7×10 ⁶ units	4	0
Larcan ³¹	1977	UK	IV	1.2–2.4×10 ⁶ units	36	0
Labauge ⁶⁶	1978	UK	IV	6–34×10 ⁵ units	37	0
Miyakawa ⁵⁰	1984	UK	IV/IA	7–9×10 ⁵ units	49	4
Total for UK 26/1,025=3% cerebral hematoma						
Yamaguchi ⁵⁴	1991	t-PA	IV	1.7–3.4 mg/day for 7 days	145	0
ASSG ⁵²	1992	t-PA	IV	12.2–44 mg	104	11
Karnik ⁵³	1992	t-PA	IA	20 mg	1	0
Bruckmann ⁷⁷	1989	t-PA	IV	25.9 mg	1	0
Yamaguchi ⁵⁴	1991	t-PA	IV	17–51 mg	58	15
Okada ²⁹	1991	t-PA	IV	26–50 mg	15	46
JTSG ¹⁷	1992	t-PA	IV	34 mg	51	8
Mori ¹⁴	1991	t-PA	IV	34/50 mg	19	10
Buteux ⁷⁸	1988	t-PA	IA	50 mg	1	0
NIH Study ^{68a,68b}	1992	t-PA	IV	50–70 mg	94	5
Hennerici ⁵⁵	1991	t-PA	IV	70 mg	18	5
von Kummer ⁵⁶	1991	t-PA	IV	70 or 100 mg	27	5
von Kummer ⁵⁸	1992	t-PA	IV	100 mg	32	9
Overgaard ⁶⁹	1992	t-PA	IV	100 mg	21	5
Turrin ⁷⁹	1991	t-PA	IV	100 mg	1	0
Wildemann ⁸⁰	1990	t-PA	IV	100 mg	1	0
Herderschee ⁸¹	1991	t-PA	IV	100 mg	2	0
Henze ⁸²	1987	t-PA	IA	100 mg	1	0
Brucker ⁵⁷	1992	t-PA	IV	100 mg	28	4
Jafar ⁸³	1991	t-PA	IV	150 mg	1	0
Total for t-PA 48/621=8% cerebral hematoma						
Grand total all drugs 81/1,781=5% cerebral hematoma						

Cerebral hematomas were diagnosed by routine computed tomographic brain scan or post mortem. Studies are listed according to drug used and increasing dose. No. of patients, total number of patients in study; ASSG, Acute Stroke Study Group; JTSG, Japanese Thrombolysis Study Group; NIH, National Institutes of Health; F, fibrinolysin; T, thrombolysin; SK, streptokinase; UK, urokinase; t-PA, tissue-type plasminogen activator; IV, intravenous; IA, intra-arterial.

due to different frequencies and timing of CT scanning after thrombolysis, different doses of drug, or inclusion of different types of ischemic stroke and thus should be

viewed with this in mind. The estimated rate of symptomatic intracerebral hematoma formation after thrombolysis (5%) is similar to the estimated expected natural

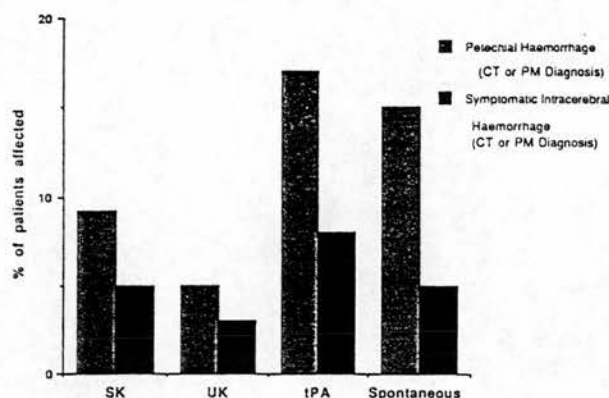


FIGURE 2. Bar graph showing comparison of the spontaneous rate of hemorrhagic conversion in cerebral infarcts with that after the use of thrombolytic drugs in acute ischemic stroke (see Tables 4 and 5 for exact figures). SK, streptokinase; UK, urokinase; tPA, tissue plasminogen activator; CT, computed tomographic; PM, postmortem.

history. The cerebral hematoma rate varies between studies and appears to be higher with t-PA (Figure 2). Although this may be due to a number of factors including differences in frequency and timing of CT scanning, postmortem rates, or different doses of drug, the trend is similar to the cerebral hemorrhage rate found when SK and t-PA were compared in ISIS-3⁸⁷ and GISSI-2⁸⁸ in acute myocardial infarction. Ascertainment of the true cerebral hemorrhage rate with each thrombolytic drug will only be possible by direct comparison in large randomized trials similar to the myocardial infarction studies.^{87,88} Two small randomized trials that compared low-dose UK with t-PA^{54,59} found no significant difference in outcome or hemorrhagic transformation rates.

The randomized trials (with CT scanning) all found massive hemorrhagic infarction slightly more often in placebo-treated than in thrombolysis-treated patients. Mori et al¹⁴ found hemorrhagic transformation of mild degree in 26% of t-PA-treated and 33% of placebo-treated patients. Ohtomo et al¹⁵ found that two of 169 UK-treated patients developed hemorrhagic transformation of the infarct of mild degree, whereas one of 181 placebo-treated patients developed a severe symptomatic intracerebral hematoma. Abe et al¹⁶ found no symptomatic intracerebral hematomas with UK. In the JTSG trial there were massive hemorrhagic infarcts in four of 51 patients in the t-PA-treated group and in five of 47 patients in the control group.¹⁷

None of the large open stroke trials found a relation between dose of drug and symptomatic intracerebral hematoma formation, but they suggested that a time delay of over 6 hours from onset,⁵² hypertension, and possibly treating patients who already had a low-density area visible on CT may be risk factors.^{55,68a,68b} Matsu-moto and Satoh⁴⁹ have treated 52 acute ischemic stroke patients with a wide range of doses of UK and have not demonstrated any definite relation between cerebral hemorrhage and dose, time after onset, or age of patient. They suggested that hemorrhages were more often symptomatic in recanalized patients, but this conclusion was based on very small numbers (Figure 3). No definite association with recanalization was found in the Acute Stroke Study Group trial⁵² or by Miyakawa and Sakuragawa.⁵⁰ Therefore, it appears that although one might expect thrombolytic treatment to increase symptomatic hemorrhagic transformation of cerebral infarcts, using the limited data available at present, the risk is of an order of magnitude similar to the estimated

natural rate. The true risk of hemorrhagic transformation of the cerebral infarct after thrombolysis can be found only by large randomized, controlled trials using serial CT scanning (or magnetic resonance imaging or postmortem series when appropriate) in all patients.

Does Thrombolysis Increase the Risk of Space-Occupying Edema Formation in the Cerebral Infarct?

The cause of severe infarct edema is unclear. It may be due to "reperfusion injury," and therefore thrombolysis might worsen this condition.⁸⁹ As far as can be ascertained, severe infarct edema is not simply due to recanalization^{90,91} and occurs naturally in approximately 5% of large infarcts.⁷¹ However, the data on symptomatic cerebral infarct edema formation are even more limited than those for hemorrhagic transformation (Table 6). The frequency of cerebral edema with brain herniation is difficult to extract from the thrombolysis studies but does not appear to be increased. Many studies did not mention severe infarct swelling, although it may have occurred. Mori et al¹⁴ found that massive brain swelling occurred in 9% of patients who reper-fused compared with 35% who did not (26% of t-PA-treated and 25% of placebo-treated patients).

We have prospectively examined reperfusion in 47 patients with partial or total MCA territory infarcts⁹²: infarct swelling was greatest in the largest infarcts and in patients whose symptomatic MCA remained occluded on angiography or transcranial Doppler ultrasound. Patients who reper-fused within the first 3 days of onset had smaller infarcts with less edema and a better clinical outcome.

What About Dose and Mode of Administration of Thrombolysis, Elderly Patients, and Time Limit to Treatment After Onset?

To avoid delay, any treatment for acute stroke must be easy to administer. The standard intravenous dose for myocardial infarction is 1.5 megaunits SK or 100 mg t-PA. Smaller intracoronary doses were used in early studies to try to maximize local thrombolytic effect and reduce systemic adverse effects, but any benefit was more than offset by the extra 1 or 2 hours of delay caused by angiography.⁹³ Intravenous administration of thrombolysis would also be quicker than intra-arterial administration in acute ischemic stroke.

If thrombolysis is to be a worthwhile treatment for acute ischemic stroke, it should be available for the

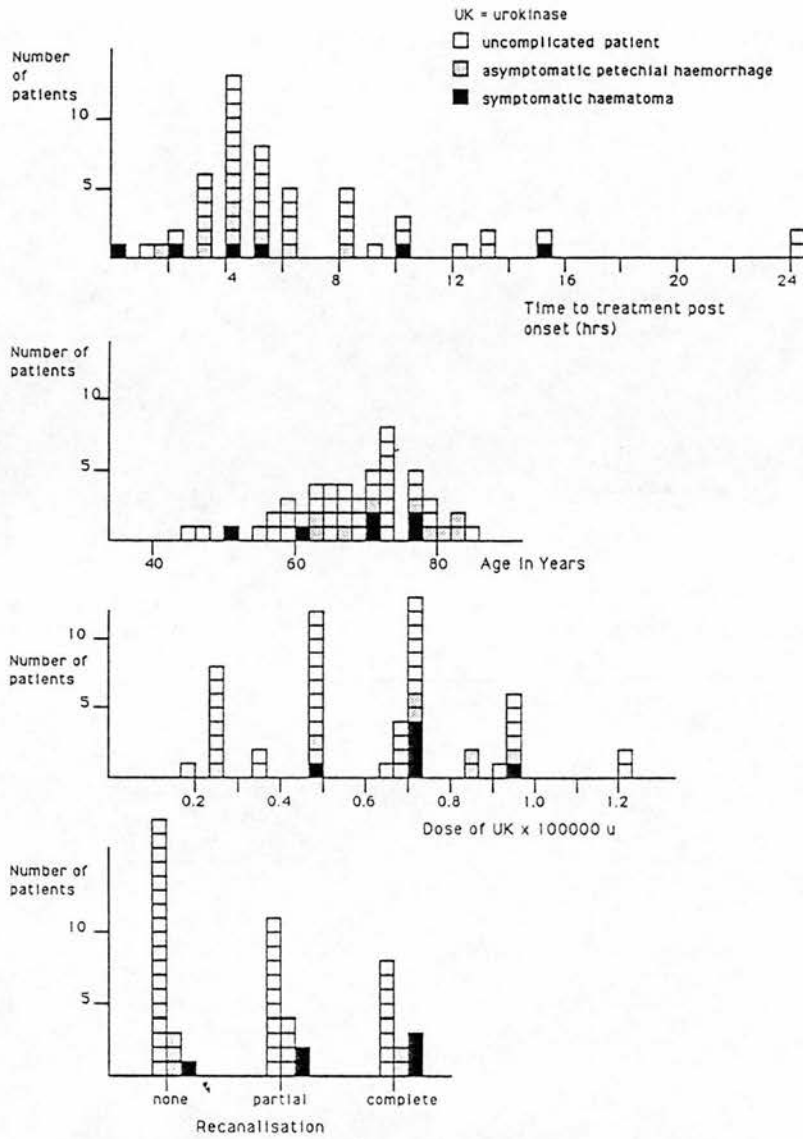


FIGURE 3. Bar graphs showing effect of time after stroke onset (top panel), age of patient (second panel), total dose of urokinase (third panel), and recanalization (bottom panel) on cerebral hemorrhagic complications. From Matsumoto and Satoh.⁴⁹

elderly, the most commonly affected age group. Cerebral amyloid angiopathy has been cited as a reason for increased risk of hemorrhage in the elderly.⁹⁴ The few studies in which thrombolytics have been used in elderly

stroke patients (aged older than 70 years) do not show a definitely increased hemorrhage rate compared with younger patients. Figure 3 shows the results of Matsumoto and Satoh⁴⁹ in patients aged up to 86 years. The

TABLE 6. Severe Cerebral Infarct Edema After Thrombolysis for Acute Ischemic Stroke

Author	Year	Drug	Route	Dose	No. of patients	Percent affected
Theron ³⁶	1989	SK	IA	0.25–1.5 × 10 ⁵ units	12	8
Fujishima ⁶²	1986	UK	IV	3 × 10 ⁵ units	143	0.7
Ikeda ⁴⁴	1990	UK	IA	4.2 × 10 ⁵ units	13	8
NIH Study ^{68a,68b}	1992	t-PA	IV	50–70 mg	74	3
von Kummer ⁵⁶	1991	t-PA	IV	70 or 100 mg	21	33
Koudstaal ⁸⁹	1988	t-PA	IV	100 mg	2	100
Mori ¹⁴	1991	t-PA	IV	34–50 mg	19	26

Total 18/284=6% severe infarct edema

Severe infarct edema was diagnosed by routine computed tomographic scan, and only studies that mentioned it as a complication have been included. No. of patients, total number of patients in study; NIH, National Institutes of Health; SK, streptokinase; UK, urokinase; t-PA, tissue plasminogen activator; IA, intra-arterial; IV, intravenous.

Acute Stroke Study Group⁵² included patients aged up to 80 years and did not find an increased cerebral hemorrhage rate in the older patients. Several other reports^{36,45,48} of thrombolysis in elderly stroke patients have shown benefit, but this is anecdotal.

ISIS-2²³ showed that in elderly myocardial infarct patients treated with thrombolysis, the proportional reduction in mortality was the same as for younger patients and the absolute reduction was greater. The elderly perhaps have the most to gain from a treatment that reduces disability from stroke, and thrombolysis certainly deserves a trial at all ages.

A time limit of 6 hours from onset to treatment was set by most of the recent thrombolysis studies, although the sparse data available do not show a sharp increase in adverse effects between 6 and 24 hours.⁴⁹ Several Japanese studies have included patients for several days after stroke with no obvious increase in adverse effects.^{15,16,59,60,67} Although it is unlikely that neurons survive many hours of ischemia, we do not really know enough about the duration of neuronal viability after acute cerebral artery occlusion to introduce time limits to treatment. Time limits can only be established by large randomized, controlled trials. In most parts of the world stroke patients go to the hospital (if at all) in a "slow ambulance," and few reach the hospital and have a CT scan by 6 hours. Although it was possible to recruit patients within 90 minutes of symptom onset in the National Institutes of Health (NIH) t-PA study^{68a,68b} (and very early recruitment is continuing in the NIH randomized, controlled trial of t-PA), elsewhere in the world it is likely to take many years to change the current slow referral pattern. Therefore, future trials should examine the problem of maximum time limit by including patients up to 24 hours after onset; otherwise, we will never know the risk/benefit ratio of thrombolytic treatment between 6 and 24 hours.

If very early treatment is the aim, is there a danger in exposing patients who are having a transient ischemic attack (TIA) to thrombolysis? Levy⁹⁵ found that 50% of TIAs last less than 30 minutes, and in patients with a deficit persisting at 60 minutes, less than 2% will resolve spontaneously in each subsequent 1-hour period. Therefore, there is very little danger in treating a TIA with thrombolysis if patients showing distinct signs of improvement in the first 1–2 hours are excluded.

Which Drug Should Be Used?

Most of the available thrombolytics have been tested in stroke, using oral, intravenous, and intra-arterial routes of administration and a wide range of doses. Table 2 shows that in the small nonrandomized studies thus far there is little difference in immediate patency rates between t-PA, SK, or UK and no obvious optimum dose. The number of patients is small, however, and there may be publication bias. Several open studies have failed to identify an optimum dose.^{49,52,56,68a,68b}

The lack of a clear benefit for one drug or dose is not unexpected. ISIS-3 and GISSI-2 combined had to randomize over 60,000 patients to show that the reduction in vascular deaths after myocardial infarction was the same whether SK, t-PA, or anistreplase was used. But there was a highly significant excess of cerebral hemorrhages with t-PA: seven of 1,000 compared with three of 1,000 with SK.⁸⁷

Although studies of thrombolysis in myocardial infarction may not be directly relevant to the use of thrombolysis in acute ischemic stroke, investigators should be aware of the now vast amount of information available from studies of thrombolysis in cardiovascular disease. Extrapolation from ISIS-3 and GISSI-2 suggests that the clinical benefit for thrombolysis in acute ischemic stroke should be about the same no matter which agent is used, but the cerebral hemorrhage rate might be higher after t-PA. Our simple analysis of the available data (Tables 4 and 5 and Figure 2) tends to support this, and certainly SK (or any of the other available thrombolytic drugs) should not be rejected in favor of t-PA without being adequately tested.

Conclusions

Experience with thrombolysis in acute ischemic stroke suggests that the risks are not excessive and there may be some benefit. However, the standard of methodology used in most of the trials thus far means that this conclusion must be very tentative and no more than hypothesis generating. It has been enough, however, to encourage Italian, Australian, and American investigators, who have recently started randomized trials of intravenous thrombolysis (SK/aspirin/both or neither, SK/aspirin/placebo, and t-PA/placebo, respectively) in acute ischemic stroke.

Considerable expertise has now accrued showing the value of thrombolysis and aspirin in acute myocardial infarction. As well as demonstrating benefit in young, otherwise healthy, myocardial infarction patients, ISIS-3 has shown that other subgroups of myocardial infarction patients, traditionally regarded as high risk for thrombolysis, gain considerable benefit from it, including the elderly and those with hypertension, previous peptic ulcer, and recent stroke.⁸⁷

It is this mass of evidence from the use of thrombolysis in myocardial infarction, as well as the limited experience in ischemic stroke, that makes it imperative and urgent to test thrombolysis properly in acute ischemic stroke. There is no place for more nonrandomized trials in this assessment. Safety cannot be assessed unless the major adverse effects of the treatment under trial are controlled for, which in this case mimic the natural history of the disease: cerebral hemorrhage and severe infarct edema.

Acute stroke treatment research is rejecting compounds thought to have therapeutic promise as fast as they can be invented, but with remarkably little good evidence to do so, and this must stop. Thrombolysis in acute myocardial infarction was almost rejected in error after innumerable small trials had missed its real benefit. It was only after the overview of these trials²² and the subsequent very large trials^{23,87,88} that the clear benefit was demonstrated, which was clear enough to change clinical practice.⁹⁶

Thrombolysis for acute ischemic stroke deserves large and methodologically sound trials designed to answer a simple question: Does it work?

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Physicians in Australia wishing to participate in an established trial should contact Dr. G. Donnan, Neurologist, Austin Hospital, Heidelberg, Victoria 3084, Australia, or in Europe Dr. L. Candilesi, Istituto di Clinica Neurologica Università degli Studi di Milano, Via F Sforza 35, 20122 Milano, Italia. In the United States the NIH multicenter t-PA trial is ongoing, and a multicenter European trial of intravenous t-PA (European Cooperative Acute Stroke Study [ECASS]) is about to begin.

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A Meta-Analysis of All Published Data on the Use of Thrombolytic Therapy to Treat Acute Ischemic Stroke

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Acute ischemic stroke is the third most common cause of death in the developed world and leaves many more patients disabled [2]. Despite this, however, there is as yet no treatment of proven benefit. Thrombolysis has been extensively tested in acute myocardial infarction (a vascular disease with some similarities to acute ischemic stroke) for which it is now an established treatment [4], having been shown to reduce the incidence of vascular death by about 25%. Thrombolysis might also improve outcome after acute ischemic stroke by speeding recanalization of occluded cerebral arteries, and reducing the amount of permanent neuronal damage.

Thrombolysis has not been extensively tested in acute ischemic stroke, although the first attempts to use it were in the late 1950's [10]. Early studies were hampered by the inability to distinguish between intracerebral hemorrhage and infarction as the cause of acute stroke symptoms, until the development of CT scanning in the early 1970's. The natural history of acute ischemic stroke is complex and the assessment of any treatment must be by randomized controlled trial, especially with thrombolysis where the likely adverse effects (cerebral hemorrhage and possible severe infarct edema) mimic the natural history of the disease. There have been more than 60 reports of the use of thrombolysis in acute ischemic stroke in the world literature so far, but we have concentrated on the published randomized controlled trials to see whether analysis using the overview technique [3] would show evidence of a beneficial or detrimental treatment effect on stroke outcome.

Subjects and Methods

We have tried to identify all published work on the use of thrombolytic drugs to treat acute ischemic stroke by a thorough literature search using Index

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Medicus, by tracing references cited in thrombolysis papers, and by discussion with other researchers interested in thrombolysis. We were able to identify 5 published trials which were truly randomized and had a control group. We have not included trials with retrospective control and prospective treated groups, nor trials where it was unclear how the control patients were selected. The overview technique was used to analyze the effect of thrombolysis on death, and on death or deterioration after acute ischemic stroke without and with the benefit of CT scanning.

Results

Five truly randomized controlled trials of thrombolysis in acute "ischemic" stroke were identified. These comprise two trials by Meyer and colleagues in 1963 [6] and 1964 [7], Abe and coworkers in 1981 [1], Ohtomo and colleagues in 1985 [9] and Mori and investigators in 1992 [8]. The two by Meyer were done prior to the development of CT scanning and may inadvertently have included patients with cerebral hemorrhage or hemorrhagic infarction as the cause of stroke rather than true ischemic strokes. Those by Abe, Ohtomo, and Mori and their respective coworkers were all done with the benefit of CT scanning.

The trials added together included a total of 601 patients. Although different drugs, dose of drug, time to treatment, type of ischemic stroke, and endpoint were used in the 5 trials, the overview (or meta-analysis) allows comparison of different trials to look for an overall treatment effect. In the case of the trials by Meyer, Abe, and Ohtomo, the published information was used, but additional information on deterioration was supplied by Professor Mori.

Analysis of all 5 trials shows that the risk of death is increased by 32% with thrombolysis (95% CI: 30% reduction to 150% excess), and the risk of death or deterioration is reduced by 26% (95% CI: 57% reduction to 27% excess). Analysis of the trials by Abe, Ohtomo, and Mori conducted with the benefit of CT scanning (and therefore truly ischemic stroke) shows a reduction in the risk of death of 40% (95% CI: 79% reduction to 70% excess) with thrombolytic treatment, and in the risk of death or deterioration a reduction of 63% (95% CI: 22% – 82% reduction). The reduction in the risk of death or deterioration with thrombolysis in the CT-guided trials is significant ($2p = 0.012$) and provides some evidence that thrombolysis is likely to be beneficial in acute ischemic stroke, and certainly needs to be properly evaluated.

Discussion

Although there is now increasing information on the use of thrombolysis in acute ischemic stroke from uncontrolled "dose escalation" studies, the data from these studies cannot be used to assess treatment, as the major adverse ef-

fects of thrombolysis – cerebral hemorrhage and severe infarct edema – were not controlled for (and in this case they mimic the natural history of ischemic stroke).

Information from recent larger randomized controlled trials of thrombolysis in acute ischemic stroke will be available in the near future. Professor Yamaguchi has presented results of the Japanese multicenter randomized controlled trial at this Symposium. Several randomized controlled trials of thrombolysis in acute ischemic stroke are planned or in progress in Europe and the USA.

However, the overview analysis of the scant information from the 5 randomized controlled trials of thrombolysis so far available provides some evidence that thrombolysis may be beneficial, certainly enough to encourage much larger randomized trials. Very large trials, on the scale of the thrombolysis in myocardial infarction studies [5] including many thousands of patients, will be needed to establish the true beneficial and adverse effects of thrombolytic treatment. Trials should allow patient entry up to at least 12 h (and possibly 24) after symptom onset because in many parts of the world stroke patients go to the hospital, if at all, in a “slow ambulance” and it is unrealistic to expect that to change overnight. Studies should include elderly patients and as wide a spectrum of ischemic stroke as possible so that the risk/benefit ratio can be identified for all age groups and types of ischemic stroke. The overview analysis has shown that thrombolysis is a promising treatment for acute ischemic stroke and provides sufficient justification for the testing of thrombolysis in large randomized controlled trials.

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